College Physiology

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Preface

College Physiology has been written to provide the foundation for students whose main interest lies in the various fields of zoology and also for those whose chief concern is with the functions of the human body alone. The zoological approach is everywhere in evidence, but emphasis is placed on functions of the vertebrate body, especially that of the human. Thus, beginning zoology students acquire sufficient knowledge of all body systems to meet the prerequisites for advanced courses; at the same time other students gain better understanding of the human body through a study of related functions in lower animals, noting the similarities and the degree of organization. Throughout all discussions a minimum of biological knowledge is assumed, each new term and subject being carefully described at its first appearance. Although clinical observations are cited, they appear only where they provide valuable illustrations of basic physiological principles.

The method of presentation used in this text has been developed through many years of teaching experience. This experience has not been restricted to zoology students alone, but has included students in pharmacy and dentistry, physical education, nursing, and teaching, as well as those satisfying science requirements. Thus, the text is not so specialized as to fit the needs of only a particular group.

The organization, like the method of presentation, has also met the test of experience. Basic principles of general physiology, including brief discussions of physical and chemical phenomena, are presented first. Then come parts devoted to skeleton and muscle, nerve, receptors, circulation, respiration, digestion and excretion, and endocrines and reproduction.

The early treatment, in Parts Two and Three, of muscle and nerve functions aids understanding of other body systems because basic principles involved in these functions apply to other systems. Of particular value is the bringing together in a single chapter of all functions of the autonomic nervous system, which greatly facilitates understanding of this important system. Moreover, because this chapter provides the reader with an appreciation of the manner in which circulation, respiration, and digestion are controlled and influenced, its early position in the book is also important. Some information is included about the newer knowledge of the secretion

of neurohormones at the tips of autonomic neurons and the part the secretions play in chemical mediation of nerve impulses

Although the circulatory, respiratory, and digestive systems receive separate treatments the interrelations of their functions are emphasized in order to bring out the coordinated activities within the body In Chapter 33 the physiological action of vitamins is discussed especially in their function as prosthetic groups in some of the enzyme systems of the cell In the chapters on the endocrine system some discussion, although brief, is given to production of hormones in invertebrates

The many illustrations, which are for the most part new, depict only essential features and omit meaningless details The references at the end of each chapter suggest sources of more detailed information than appears in this text and include some original articles as a guide to students wishing further information on subjects of particular interest However, because reference material is largely superfluous for beginning students the lists have been kept brief

We wish to acknowledge the conscientious efforts on the part of Mrs Georgia Nimie, who prepared most of the illustrations, of Mrs Elaine Joyce Aftonomos for Figures 6, 161, 184, 189, 198, 201, 218, 251, 255, 290, 291, 298, and 304 of Mr Marvin Malone, for Figures 9, 46 70, 94 163 183, 243, and 302, and of Mrs Betty Zieg whose patience in typing and arranging the manuscript and in performing the many rather menial but important labors that are part of the job of preparing a text for publication

We are indebted to those colleagues who have, from time to time, offered suggestions regarding the manuscript We are especially indebted to Dr Harald G O Holck who contributed greatly in reading the manuscript and who offered many constructive criticisms We also owe our thanks and gratitude to our wives, Norma H Pace and Glen B McCashland without whose patient efforts and willingly accepted extra responsibilities our work would have been much more difficult

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Introduction

PHYSIOLOGY, in the broader sense, is a study of the functions of cells, tissues, organs or organisms. In this study, an attempt is made to understand how and why living things behave as they do. Many years ago, man concerned himself mainly with studies of gross structure. However, as he gained familiarity with these things, and as new methods and equipment—such as anesthetic agents and the microscope—became available, he was able to observe internal structures functioning within the living body and even to study the finer details of body architecture. There are now means available for studying even submicroscopic components of living materials. Today's student in physiology is indeed fortunate that such progress has been made, and that he may benefit, in a study of comparatively short duration, from the results of centuries of painstaking investigation. In the following pages, the important features of physiology, as it is of greatest concern to the beginning student, are presented as an introduction to this extremely interesting field.

Complete separation of physiology from other sciences is frequently difficult and sometimes impossible. Since physiology deals with living things it is considered a biological science. Plant physiology closely parallels animal physiology, but the latter is of main concern to us in our present work. Anatomy, a study of structure, must be understood before function may be properly appreciated. Gross anatomy concerns itself with larger structures, while microscopic anatomy, or histology, deals with structure of tissues and cells.

While we may be able to observe a living organism in action, it is quite essential that we know how, and even attempt to explain why, such actions take place. Eventually chemistry and physics become important in such problems. For our purpose here, however, only the essentials of these two fields will be presented as required for the basic material which we are to consider. Nevertheless, the importance of chemistry and physics increases as the scope of physiological study is expanded.

The results of all of these studies—physical, chemical, and physiological—have demonstrated that the functions of a highly complex organism may be an integration of smoothly running systems each composed of count

less numbers of cells. These cells are the smallest functional units of the living body, and are capable of displaying all of the basic phenomena of life as seen in the larger organism. It would seem natural then, if a study of the living body were to have meaning, that the characters of structure and function of the cell should be given first attention, and since these cells are influenced by the conditions of their external and internal environment, consideration must be given to the physical and chemical factors which will be of importance for a physiological study. It is with this in mind that this book has been written, attempting always to recognize the integration of these basic units into a proper relationship with one another so that the normal function of the entire organism may be effectively accomplished.

Part One

GENERAL

1

Basic Phenomena of Living Organisms

THE CELL

THE TERM *cell* was first used by Robert Hooke, who published a monograph in 1665 concerning his observations of many objects seen under his microscope. This was some 60 to 80 years after the invention of the microscope. He had observed boxlike structures in a thin slice of cork. Cork is dead material and actually what Hooke saw were the cellulose walls. They reminded him of cells in a monastery.

Biology teaches that the cell is the unit of structure of all living things. This is the so called cell theory, which, according to most textbooks, was first proposed in 1838 and 1839 by Schleiden, a botanist, and Schwann, a zoologist. Although credited with originating this theory, in reality these men were only instrumental in popularizing a general trend of thinking initiated years before their time by numerous authors and investigators.

Structure of Cells

All living cells resemble one another in a general way. Many components and many physiological processes are common to all. A cell is a mass of protoplasm containing a nucleus. Protoplasm consists of cytoplasm (the living substance surrounding the nucleus), nucleoplasm (the nucleus itself), and the cell membrane which surrounds the whole mass. This membrane is said to be selectively permeable because it appears to have control over those molecules or substances that may enter or leave the cell. The cytoplasm and nucleus are made up of many constituents, some of which are represented diagrammatically in Figure 1. Plant cells often have *vacuoles* within them. These are spheroid or ellipsoid areas, definite in outline, surrounded by a membrane, and containing a fluid consisting chiefly of inorganic salts but with a little organic material dissolved in it. In plants the volume of the vacuole may exceed that of the cytoplasm. Aside from that of certain protozoans, cytoplasm of animal cells does not usually have pronounced *vacuoles*. Plant cells often contain *plastids* of one type or another, which produce certain substances, such as starch, within cells. *Chloroplasts*, which contain *chlorophyll*, are shown in the figure of the plant cell. Colorless plastids, called *leucoplasts*, may also be present. Chloroplasts are the most impor

tant of the plastids Chlorophyll, when properly associated with other organic catalysts within the chloroplasts, is the substance which has the power to transform the radiant energy of sunlight into the chemical energy of the starch grain, the starch is produced from carbon dioxide and water within the chloroplast Leucoplasts also form starch but must have access to preformed simple organic compounds in order to do so, they cannot transform carbon dioxide and water

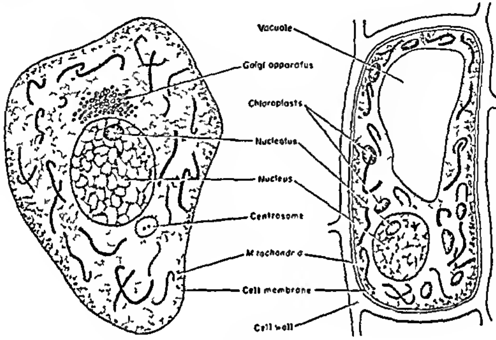


FIGURE 1

Comparison of an animal cell (left) with a plant cell (right).

There is also found within cytoplasm, at one pole of the nucleus, a *centrosome* which functions during cell division It consists of a central granule, called the *centriole*, and the surrounding alveolar like material called the *centrosphere* During nuclear division the centrosome divides and may aid in the movement of the chromosomes It should be noted that a centrosome does not exist in all cells, but mainly in most animal and lower plant cells

Mitochondria, which play a part in metabolic processes, and *Golgi bodies* are also present in most living cells, the former as rods or granules and the latter as many small globules There is some evidence that the Golgi bodies function in the secretory and respiratory processes within the cell

Also found in cells are numerous types of food materials and other substances, which are stored in the form of crystals and granules

Certain organic substances, which are similar in their function to inorganic

catalysts in that they initiate or accelerate chemical processes, are also present. These *enzymes* are discussed on page 24

All these substances are present in the material that we refer to as protoplasm of which living cells are composed Protoplasm is not, therefore, as homogeneous as it appears to be at first glance

Physical Properties of Protoplasm

Comparatively little is known about protoplasm It is known that protoplasm is never the same from one moment to the next because chemical and physical processes are continually going on for the maintenance of life itself In other words, the processes never come to an equilibrium as long as the organism is in a living condition

The ground substance of protoplasm is composed chiefly of protein However, many proteins, amino acids, carbohydrates, fats, inorganic salts, possibly hormones, vitamins, and water are closely associated in the functioning of living protoplasm Protoplasm is not a mixture of these substances, they are all integrated within the protoplasmic mass to make up an organized whole, which is referred to as the living cell

Protoplasm is sometimes fairly transparent and varies considerably in its consistency in different cells or even in the same cell from time to time Its viscosity (page 12) usually approximates that of glycerin and is seldom less than that of machine oil

THE FUNDAMENTAL PHYSIOLOGICAL PROPERTIES OF LIVING MATTER

Although certain substances—the viruses, for example—remain unclassified, the following definite physiological properties of protoplasm may be used to distinguish living from nonliving matter

1 *Contractility* is possibly a property of all protoplasm (streaming, amoeboid, ciliary, and muscular movements are all manifestations of contractile phenomena)

2 *Irritability*, the ability to respond to a stimulus really involves a change in rate or kind of processes occurring on the surface of or within a cell

3 *Conductivity* is the progressive transmission of the changed condition over the cell, specialized within the nerve as the impulse

4 *Metabolism* is the sum of all the chemical processes going on within a cell, tissue, or organ, sometimes metabolism is applied to specialized types of reactions, such as cellular, muscle, or liver metabolism

5 *Growth*, which is usually associated with metabolism may be evidenced by an increase in the total mass of protoplasm within the cell, tissue, or organism In living matter growth occurs by *intussusception*, or building up of new material by combinations of smaller molecules, such as the forma

tion of proteins from amino acids Sometimes growth is described as an increase in numbers, but this is true growth only when accompanied by an increase in mass Thus *growth should* be carefully *differentiated from* reproduction In nonliving matter, on the other hand, crystals of inorganic salts are said to grow by *accretion*, which is the piling up of numbers of the same kind of molecules without change in molecular structure For example, sodium chloride crystals form as the water evaporates from a sodium chloride solution, the crystals get larger and larger, but they continue to consist of sodium chloride molecules No new substance has been formed

6 *Adaptation* is the ability to modify behavior in accordance with a change in environment

7 *Reproduction* is the ability of cells and organisms to reproduce in kind

8 *Spontaneity* is autonomous (automatic) activity on the part of a living system Although classifying spontaneity as a *property is questionable*, many scientists claim that the ability of protoplasm to carry out automatic changes is a characteristic of living matter

All or most of these properties may be found in living systems A few of them may be found in nonliving substances—crystals "grow," and electrical devices are "irritable"—but many of them never appear in any one nonliving system

There are many criteria by means of which we attempt to judge whether matter is living or nonliving However, in some cases it is difficult to say whether life does or does not exist For example, the viruses, which are submicroscopic agents responsible for many different infectious diseases in plants and animals (tobacco mosaic, common cold, etc), have not yet been classified as living or nonliving They may be constituted of protein which displays some characteristics normally observed in living material

COMPARISON OF GENERAL AND SPECIALIZED CELLS

The characteristics and properties of living matter described above are found in all cells both general and specialized The amoeba, a complete organism in itself, has no specific function and is an example of a general cell It has all of the fundamental physiological properties of living matter it contracts, conducts impulses over its surface, takes in food material, oxidizes glucose, grows, and reproduces A specialized cell, such as a muscle cell, functions in the same manner, with the exception that it has one specific function—contraction—that it performs better than any other A similar comparison may be made between an amoeba and a gland cell, or between an amoeba and a mammalian egg cell

All protoplasm is not, however, specifically similar, as is known from ob-

servation For example, muscle cells differ from nerve cells, gland cells, connective tissue cells, and amoebic because they are made up of different types of protoplasm In fact as was previously stated, because of the constant activity and the continuous chemical changes that take place in it, even a particular mass of protoplasm is different from one moment to the next

PHYSICO CHEMICAL PHENOMENA ASSOCIATED WITH LIVING SUBSTANCE

From the definition of physiology, it is obvious that at least an elementary knowledge of some of the physical and chemical phenomena that are associated with the activities of protoplasm is essential to an understanding of fundamentals of this branch of biology Such phenomena are important to all living substance and consist of surface energy or surface tension adsorption, the colloidal state, viscosity, diffusion, and osmosis

Surface Energy

The energy produced at cell surfaces due to molecular action is known as surface energy, or surface tension All living cells have surfaces, and much of a cell s behavior depends upon the condition of its surface and the relation of that surface to the surrounding tissue fluid (or other medium in the case of lower organisms) The interaction between the cell s surface and that of the tissue fluids or other watery media which it contacts creates surface tension That is surface energy or surface tension is not a property of one surface but of two surfaces and as long as these surfaces exist, or as long as the two liquids do not mix, the surfaces exhibit energy Surface energy is exhibited not only by liquid liquid surfaces but also by liquid gas liquid solid, gas gas, and so forth

The fact that an ordinary steel sewing needle floats on the surface of water in a drinking glass is common knowledge As long as the needle is clean it will float even though the specific gravity of steel is much greater than that of water It appears as though a film exists at the surface This is actually true and can be explained as follows

A beaker of water contains countless numbers of water molecules These molecules have two forces acting upon them (a) a repellent force because the molecules are in motion, and (b) an attraction force, by means of which all the molecules tend to remain together in a body Referring to Figure 2, one can see, then, how all the molecules in the body of the liquid attract one another with equal force Those at the surface, however, are attracted unequally That is there are comparatively few water molecules above the surface to attract those at the surface Consequently, the mole

cules beneath the surface tend to pull those at the surface downward which produces a more rigid layer or film

These molecular forces act equally within a fluid mass and cause it to take on a spherical shape which presents a minimal surface That is a

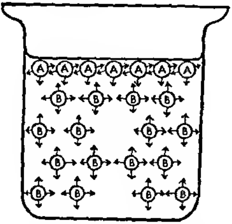


FIGURE 2

Illustrating the way in which molecules within a body of water attract those at the surface producing a surface film A molecules at surface B molecules below surface exerting pull on surface molecules

sphere has less surface than any other shape of equal volume Because of surface tension all fluids tend toward a minimal surface Other forces may often prevent fluid matter from becoming truly spherical but the tendency is there just the same Water dripping from a faucet takes on a raindrop shape because of the action of gravity cells in our bodies tend to take on a spherical form but other forces cause many of them to be cubical hexagonal elongated or some other shape

Surface tension is associated with many vital phenomena The different types of movements are at least partly influenced by surface tension changes as are cell division permeability and excretion

Also associated with contact of surfaces is an electric potential or charge *between the two surfaces* It is not clear why a charge occurs but the cause is probably dissociation of molecules at the surface The relation of this electrical phenomenon to nerve stimulation and conduction is described more fully in Chapter 8

Adsorption

A surface phenomenon in which one substance may adhere to the surface of another is known as *adsorption* Chemical reactions take place at these surfaces We know this to be true especially for enzymatic reactions that go on within cells or living organisms Enzymes present surfaces to those molecules which they attract and catalyze in their reactions

Adsorption may be defined as *the tendency of molecules or ions to con*

centrate at a surface. Adsorption is distinguished from *absorption* by the fact that the former concerns the collecting of materials on a surface, by adhesion, whereas the latter is concerned with capillary forces or cohesion. For example, protein molecules may become adsorbed or concentrated at the surface of proteolytic enzymes, but water is absorbed into and fills the capillaries of a sponge or blotter.

The Colloidal State

Much of the material of living matter as well as many other substances of physiological interest is in what is called the *colloidal state*. The term *colloid* (meaning gluelike) was introduced in 1861 by Thomas Graham, an Englishman, who wished to distinguish between gluelike substances which do not crystallize, such as egg albumin, and those substances that do, such as salt. Actually, the term is erroneous since many of the substances formerly thought to be noncrystallizable can now be crystallized, and vice versa.

Because matter in the colloidal state is difficult to visualize the following illustration may be helpful. If a cube of solid matter, such as gold,

TABLE 1

Micrometric Equivalents

1 inch	=	(approximately) 2½	cm (centimeters)
1 cm	=	10	mm (millimeters)
1 mm	=	1000	μ (microns)
1 μ	=	1000	mμ (millimicrons)
1 mμ	=	100	μμ (micro microns)

of 1 mm. edge, is placed in water and divided into one billion cubes of 1 micron edge (see Table 1 for micro measurements), these cubes will immediately sink to the bottom of the container. If looked at under high power of the microscope, the individual cubes can be seen. Now, if one of these cubes of 1 micron edge is further divided into one million smaller cubes of 0.01 micron (or 10 millimicrons) edge, the resulting particles no longer sink and cannot be seen under the microscope (the limit of microscopic vision is approximately 0.2 microns, that is, the diameter of the smallest object one can see with the aid of the highest powered compound microscope is about 200 millimicrons). These gold particles, which remain suspended are said to be in a colloidal state. Small though they are, however, these particles are far larger than molecules. Thus a colloidal solution differs from a true solution in which there is complete separation of the molecules

a colloidal solution is a suspension of molecular aggregates Colloidal particles may, however, vary in diameter from 1 to 100 millimicrons

Although these colloidal particles cannot be seen with the highest microscopic magnification, their reflection can be seen by means of the ultramicroscope The principle is the same as that which enables one to see rays of light in a darkened or shaded room The rays of light are not actually seen but rather, the reflection from the dust particles lying in their path and if the room were absolutely free of dust one would see only the reflection from a spot on the floor where the light rays strike In the ultramicroscope, the rays of light enter the field at an angle such that they are reflected by the colloidal particles

Protoplasm is in the colloidal state, as are also practically all the fluids of the body such as blood, tissue fluid, milk, digestive secretions, humors of the eye, cerebrospinal fluid, and others

Viscosity

Protoplasm being a colloid may vary in its consistency, or viscosity, just as other colloids may The same solution may be quite fluid at one moment and jelly like the next, and the change may be either reversible or irreversible Solutions exhibiting the more fluid condition are referred to as *sols*, those exhibiting the jelly like condition, *gels* Although it is difficult to draw a sharp line between a sol and a gel at the point where a change over is made, there are many grades of fluidity between the extreme sol and extreme gel states In the transition from sol to gel the solution becomes less fluid, that is, its *viscosity* increases *Viscosity* may be defined as *the resistance of matter in the liquid or semiliquid state to a change in shape* It is probably the result of internal friction of molecules Most persons are acquainted with changes in, and the effect of environmental factors upon, viscosity For example, molasses flows readily in July heat but not in January cold

Streaming and amoeboid movement, permeability, growth, mitosis, reproduction, and other processes are all affected by the viscosity of protoplasm

Diffusion and Osmosis

Diffusion is the continuous movement of molecules in a gaseous, liquid or solid state from an area of greater to one of lesser concentration, until they are equally distributed throughout the entire accessible region Everyone has observed the manner in which gases diffuse, such as the movement (diffusion) of smoke through the air until it becomes so scattered that it is no longer recognizable (the smoke itself is made up chiefly of carbon particles which are so fine that they diffuse in the same manner as gaseous

molecules). Molecules are in a continuous state of motion; they move about and collide with one another and bounce in different directions. As a consequence, in time, there would be an equal distribution of these molecules throughout the accessible space, due to chance alone.

True diffusion is not so well known in liquids as in gases because in everyday life we hasten the process by stirring. For instance, it would take too long for sugar which has been added to a cup of coffee to diffuse throughout the liquid; therefore, we use a spoon for stirring. If a crystal of a colored, soluble substance, such as copper sulfate, is carefully placed in one corner of a container of water, the diffusion process can be followed readily by change in color of the water. Under these circumstances, it takes a long time for complete diffusion to take place. The copper sulfate molecules must first dissolve and then migrate and since molecular movement is not so rapid in the liquid state as in the gaseous, this migration takes considerable time. Finally, however, the copper sulfate molecules become equally distributed and diffusion is complete. Although the molecules have come to an equilibrium insofar as numbers per unit volume are concerned, their continued motion creates a force or pressure (*diffusion pressure*). In solutions separated by membranes, this diffusion pressure may result in a phenomenon known as *osmosis* and the pressure itself is called *osmotic pressure.*

If water is separated from a sugar-water solution by a membrane permeable only to water molecules and not sugar (that is, semipermeable), osmosis makes its appearance and the arrangement of solutions and membrane constitutes an osmotic system.

Figure 3 illustrates an osmotic system consisting of water and sugar-water solutions separated by a semipermeable membrane. Both the sugar and water molecules are in constant motion and since the pores of the membrane are only large enough to permit passage of water molecules, there is, within a few hours, a noticeable change of volume of solution on either side of the membrane. This may be explained as follows: Both sugar and water molecules are striking the membrane on the left side of the container whereas only water molecules are doing so on the right side. Therefore, the number of water molecules that would pass through the pores (by chance) from the right to the left side would be greater than the number that would flow in the opposite direction. As a result, the solution on the left increases in volume and the sugar solution becomes less concentrated.

Eventually, the weight of the greater volume of fluid on the left side of the membrane will be sufficient to put an end to the unequal exchange, so there is no further increase in its volume. The pressure developed on

the left side, owing to the weight of the column of solution, is the osmotic pressure of that portion of the system, that is, it is the pressure required to prevent entrance of water molecules from the right. The osmotic

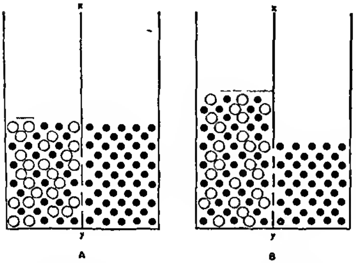


FIGURE 3

Osmosis. A, a sugar solution is placed on one side of a semipermeable membrane and pure water on the other. B, because of unequal diffusion (sugar molecules cannot pass through the membrane) there is an increase in volume on the more concentrated side. Circles, sugar molecules; dots, water molecules; xy, semipermeable membrane.

pressure of solutions actually varies inversely with the rate of diffusion of their water molecules through a semipermeable membrane into a solution of different concentration.

Diffusion and Osmosis in Relation to Living Protoplasm

The two processes, diffusion and osmosis, are commonly found in living systems. In fact, the phenomenon of osmosis was first discovered as the result of experiments with plant cells. Plant cells are observed to shrink when placed in strong sugar solutions. Because the cell membrane is impermeable to sucrose, more water molecules flow out of the cell than flow in, exactly as described above, and the loss of water causes the cell to shrink from the rigid cell wall of the plant—a phenomenon known as *plasmolysis*. The same reaction also occurs in animal cells but is less noticeable because there is no cell wall away from which the cell can shrink. By measuring cell volume, however, one can readily note that the animal cell decreases in volume when placed in a strong sugar solution.

Osmosis can take place in either direction through a cell membrane. The water molecules always move more rapidly (actually in greater numbers) from the point of their greater concentration (that is, weaker sugar solution) to that of a lesser concentration (a stronger sugar solution). If water molecules, or other small molecules, enter the cell more rapidly than they pass out of the cell, the process is called *endosmosis*, the reverse is *exosmosis*.

If one wishes to examine cells with a microscope, it is desirable, of course, to preserve their natural size and shape. In order to do this, the cells are placed in a solution which has an osmotic or diffusion pressure equal to

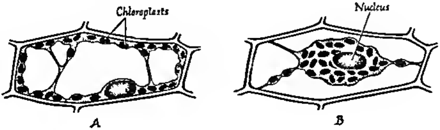


FIGURE 4

A a single cell of the plant *Elodea* under normal conditions B same cell showing plasmolysis when exposed to high glucose concentration (From Pauli *The World of Life* by permission of Houghton Mifflin Co)

that of the protoplasm. Water then passes equally in both directions into or out of the cell, and the cell volume does not change. Such a solution is called *isotonic* (isosmotic). If the cells were in a *hypotonic* solution, endosmosis would occur and the cell would swell. On the other hand a *hypertonic* solution would have a greater osmotic pressure than the cell interior so that exosmosis would occur with resultant shrinkage of the cell

Dialysis

The process of dialysis, like osmosis, depends upon the semipermeability of a membrane, and a simple example will serve best to explain it. If a solution containing protein and salt is placed within a collodion sac and the sac placed in water, the salt diffuses out of the sac into the surrounding water for the pores of the membrane are sufficiently large to allow free passage of the small salt molecules and ions. The protein molecules on the other hand, being too large to pass through the pores remain within the sac. Eventually therefore the sac contains a pure protein solution. This process of separating dissolved particles from a colloidal suspension is known as *dialysis*. It is very frequently used to prepare pure proteins and may function to some extent in the formation of body fluids from the blood

THEORIES OF CELL PERMEABILITY

Up to this point in these discussions membranes, as far as their permeability to various substances is concerned have been treated as though they were sievelike with pore size the only factor governing the passage of substances

through them. Actually, however, membranes of living cells are much more complex than artificial membranes, and although pore size does play an important part in permeability of living membranes, many other factors must be taken into consideration.

Among the numerous theories that have been advanced in regard to cell permeability, the sieve, lipoid-solubility, adsorption, and molecular theories are the more acceptable.

1. The *sieve theory* suggests that membranes act as sieves. Although this theory seems to hold to some extent for substances of small molecular size, as in the preceding examples, many substances made up of large molecules also seem to penetrate cells with ease. Therefore, the sieve theory does not explain completely the passage of substances into or out of cells.

2. The *lipoid-solubility theory* was suggested by Overton in 1891 after he had found that of all the substances he tested, those that were fat-soluble passed through the cell membrane most readily. It is known that the cell membrane is made up chiefly of lipoids (fatlike substances) and it is clear that any substance soluble in the lipoid may pass into the cell. However, the existence of some large molecules that are not lipoid-soluble but still pass through cell membranes limits this theory as an explanation of cell permeability.

3. The *adsorption theory* was postulated to explain the passage of large non-lipoid-soluble molecules through cell membranes. These molecules may become adsorbed to the lipoid material of the membrane. They supposedly pass into the cell eventually by means of the constant movement of the colloidal particles which make up the membrane.

4. The *molecular theory* has been advanced because many investigators have found that cell membranes are much more permeable to undissociated molecules than to ions. For example, hydrogen sulfide (H_2S) molecules pass through cell membranes much more readily than sulfhydryl ions ($\cdot SH$), and acetic acid creates a stronger sour taste sensation than does hydrochloric acid, although the latter breaks down to form ions more readily. The assumption is that the acetic acid molecule passes more readily into the cell.

There are many exceptions to all the theories mentioned. It has been suggested that perhaps all of them could be included in a single theory, especially if we assume a membrane structure similar to that suggested in Figure 5. The membrane would consist of relatively large lipoid micelles (spheroidal submicroscopic fat particles) packed rather closely but with "bound" water and "free" water spaces (pores) between them, arranged in a mosaic-like pattern.

Actually all the theories presented here might be incorporated in order

to explain cell permeability. Thus the sieve theory may account for the passage of molecules of small size through the "free" water pores, lipoid soluble substances can pass through by dissolving in the micellae of the membrane, and large molecules which are not fat soluble can become ad-

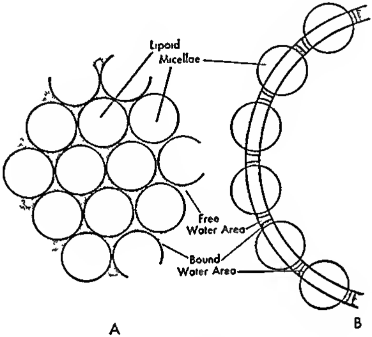


FIGURE 5

An exaggerated diagram of hypothetical cell membrane A as viewed from the surface B in cross section

sorbed to the surface of the micellae, which, by their movement, will sooner or later carry the adsorbed molecules to the inside, small undissociated mole cules because they are not "repelled" by the charges at the free water bound water surface of the "pores" will pass through readily

IMPORTANCE OF WATER TO PROTOPLASM

The physiological importance of water can be judged by its abundance in living protoplasm The human brain consists of 82 to 85 per cent water, muscle, 75 to 78 per cent, thyroid gland, 77 to 82 per cent, and some jellyfish are about 99 per cent water The necessity of water to protoplasm becomes evident when one attempts to release much of the water, an organism can lose only a comparatively small amount without being killed

Water is important primarily because of the following properties (1) *solvent power*—water is one of the best solvents known to man, (2) *low internal friction*—that is, water has a low viscosity, which is a factor in the

consistency of many of the body fluids even though they may contain large quantities of dissolved colloidal materials, (3) *high surface tension*—this tension, which is greater than that of any other liquid except mercury, may play a part in protoplasmic movement and aids cells in maintaining their structure and form (by surface tension a film of molecules is concentrated at the cell surface to aid in formation of the cell membrane), (4) *high heat capacity*—as it requires more heat for a 1 degree C increase in the temperature of water than of any other substance except liquid ammonia, water, by its heat capacity, may act as a buffer between sudden and extreme changes of external temperature and thereby serve as a protective agent, (5) *high conductivity for heat*—although this capacity is much lower than that of metals, water can conduct heat more efficiently than any other liquid and than most solids, (6) *ionization*—water, a medium in which ionization takes place readily, is of great importance in many reactions, especially hydrolytic reactions

ENVIRONMENTAL FACTORS AFFECTING LIVING SYSTEMS

Electrolytes and Nonelectrolytes

Both electrolytes and nonelectrolytes are extremely important in the environment of living systems *The typical electrolytes are the inorganic* acids, bases, and salts They are called electrolytes because their water

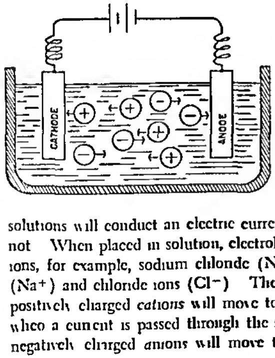


FIGURE 6

Electrolysis As an electric current passes through a solution of sodium chloride (NaCl) the positively charged ions (Na^+) or cations move to the cathode and the negatively charged ions (Cl^-) or anions to the anode (Redrawn from *The Human Body and Its Functions* Revised Edition by C H Best and N B Taylor By permission of Henry Holt and Company Inc Copyright 1948)

solutions will conduct an electric current, although pure water itself does not When placed in solution, electrolytes dissociate into their respective ions, for example, sodium chloride (NaCl) dissociates into sodium ions (Na^+) and chloride ions (Cl^-) These ions bear electric charges The positively charged *cations* will move toward the cathode (negative pole) when a current is passed through the solution containing them, and the negatively charged *anions* will move toward the anode (positive pole)

Familiar cations are Ca^{++}, Mg^{++}, Na^{+}, and K^{+}, and some common anions are Cl^{-}, SO_4^{--}, and PO_4^{---}

The organic acids and bases show only a weak tendency to dissociate into ions, and most organic compounds are therefore considered nonelectrolytes Their dissociation is either very feeble or not detectable, and they will not conduct an electric current through the solution

Hydrogen and Hydroxyl Ions

Two of the most important ions to consider in nature are the hydrogen (H^+) and hydroxyl (OH^-) ions A solution containing an excess of hydrogen ions over hydroxyl ions would give an acid reaction, on the other hand, an excess of hydroxyl ions would result in an alkaline or basic (these terms are used interchangeably) reaction Hydrogen or hydroxyl ions are produced as follows

$$HCl \rightleftharpoons H^+ + Cl^-$$

$$NH_4OH \rightleftharpoons NH_4^+ + OH^-$$

The hydrogen (or hydroxyl) ion concentration,—that is, the acidity (or alkalinity of a solution—is expressed in so called *p*H (or *p*OH, POH) units (the symbol *p*H was derived from hydrogen potential), *p*H units range from 0 0 to 14 0

Acid Range *Alkaline Range*

0 0 1 0 2 0 3 0 4 0 5 0 6 0 7 0 8 0 9 0 10 0 11 0 12 0 13 0 14 0

Urine | Blood

Pure Water

(Neutral)

Pure water, which is neither acidic nor basic, has a *p*H of 7 0, or a neutral reaction The lower the *p*H unit, the greater the acidity or H^+ concentration—for example, *p*H 6 0 indicates an acid reaction but not nearly as great as *p*H 4 0 The greater the *p*H unit above *p*H 7 0, the greater the alkalinity

Importance of Hydrogen (H^+) and Hydroxyl (OH^-) Ions in Living Systems

Hydrogen and hydroxyl ions have very definite effects on protoplasm Sometimes the effects are produced when only slight changes are made in the H^+ or OH^- concentrations

Sea water has an alkaline reaction (approximately *p*H 8 0 to 8 4) that remains surprisingly constant and is therefore an excellent medium for smaller organisms that are directly influenced by the chemicals and ions of their surroundings Too great a change in *p*H would result in death of these organisms The blood of vertebrates is also alkaline and of constant

*p*H In most vertebrates any appreciable change in the hydrogen ion concentration of the blood has dire effects on the animal This is especially true in birds and mammals a change in *p*H affects respiration as well as other functions In other words, the organ systems of complex animals are so interdependent that slight changes in one (such as *p*H changes in the blood) may result in malfunctioning of others, even to the extent of bringing about the death of the organism

Individual cells however, such as those in tissue culture (tissue cells cultivated outside the body) or protozoan populations, are not very sensitive to slight *p*H changes Some cells in tissue culture can grow in media with *p*H values between 5 5 (acid) and 8 5 (alkaline), and some micro organisms will continue to live in solutions covering an extremely great range of *p*H values, *Euglena*, for example will live at *p*H values from 2 3 to 11 0

In many cases where cells are not sensitive to changes in *p*H, the rate of penetration of hydrogen or hydroxyl ions may be so slow that the protoplasm has time to neutralize their effect Some cells are more permeable to ions than others smooth muscle, for example has been found to be very sensitive to changes in *p*H It is suggested that the great effect of *p*H changes on blood vessels may be owing, chiefly, to the action of the smooth muscles in their walls

Buffer Solutions and Body Fluids

Fluids such as sea water, blood, and tissue fluid, can maintain a fairly constant acidity or alkalinity even when acted upon by acids or alkalies This property is the result of the presence of certain types of salts and organic compounds that are called buffers For example, various phosphates such as the tri, di, and monopotassium phosphates (K_3PO_4 K_2HPO_4 and KH_2PO_4) the carbonates and bicarbonates (such as Na_2CO_3 and $NaHCO_3$) and protein compounds are excellent buffers Nature seems to have supplied them in quantity in natural fluids which require stabilization, such as the blood and sea water Such salts can be used in the laboratory to prepare buffer solutions for culture work For example, the addition of K_2HPO_4 (which has an alkaline reaction) and KH_2PO_4 (which has an acid reaction) to a solution in equal quantities produces a *p*H value of 7.0 Then if a small quantity of acid or alkali is added the *p*H of the solution does not change appreciably because the alkaline phosphate salt tends to take up the hydrogen ions and the acid salt absorbs hydroxyl ions In the protein molecule buffer action is accomplished by the amino and carboxyl groups The amino group ($—NH_2$), reacts with acids and prevents them from ioniz

ing, the other, the carboxyl group (—COOH), similarly neutralizes alkalies Hemoglobin and the plasma proteins aid in the maintenance of neutrality of the blood because of the buffer action of the amino acids in their molecules

Relation of Temperature to Living Substance

Protoplasm generally can live and carry on life functions only within a very narrow range of temperature (Figure 7), although some types of protoplasm can withstand much greater changes than others Cysts of certain unicellular plants and protozoan species and spores of bacteria are especially resistant to high temperatures as well as low In the formation of cysts and spores much water is lost by the protoplasm, and the degree of resistance evidently depends upon the amount of water lost, the lower the water content, the greater the resistance Some species of algae (a unicellular plant species) are said to live in water at 70 to 80 degrees C Amoeboid types have been found in hot springs at 50 to 54 degrees C There are also a few species of plant and animal cells that show considerable resistance to cold temperatures Pollen grains have been found to withstand temperatures around —270 degrees C for several hours, and the alga *chlorella* will continue to live after an hour s exposure at —182 degrees C

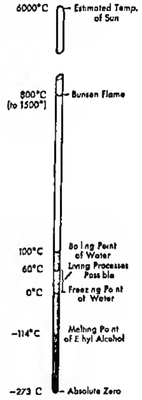


FIGURE 7

Temperature range at which life exists compared to other known temperatures

Despite these exceptional cases, however, it is generally true that organisms cannot withstand temperatures far different from those at which they normally carry out their life processes If the temperature surrounding protoplasm becomes too high, its living processes soon cease owing to *heat death* Although heat death, for the most part, appears to be the direct result of coagulation of the living protoplasm of the cell, organisms sometimes survive temperatures higher than those which would cause coagulation Moreover, some animals and plants which live at rather low temperatures may die as the result of a sudden rise in temperature to 20 to 25 degrees C, and even less There are undoubtedly other factors involved in the reaction of protoplasm to temperature changes aside from coagulation

Cold *death* results from the formation of ice crystals within a cell. If a cell is supercooled, it does not usually die unless ice crystals suddenly form within its protoplasm.

Although some more complex organisms will survive body (or cell) temperatures below freezing, many of them die if their bodies are subjected to temperatures lower than normal even though still far above freezing. Birds and mammals are especially sensitive to lowering (or raising) of body temperatures. The rabbit, for example, dies if its body temperature is lowered to approximately 20 degrees C. Here, again it is seen that the complex organism is unable to withstand a change that its individual parts can endure. Tissue cells will live and grow over much greater ranges of temperature than the body as a whole.

Relation of Light to Living Substance

Colorless animals and plants are not directly dependent upon sunlight for their existence. They are, however, indirectly dependent upon it since with few exceptions, all organisms without chlorophyll must obtain their food material from organic matter that has been formed by the action of sunlight on plants. The carnivorous animals have a similar indirect dependence for they obtain their "plant synthesized" food at second (or even third or fourth) hand; they feed upon other animals which, in turn, may be herbivorous. Some workers think that colorless organisms were the first to make their appearance on earth and that chlorophyll appeared only after the sun's rays began to break through the dense atmosphere surrounding the earth. Even today there are several species of bacteria that possess the ability to form protoplasm from carbon dioxide, water, and inorganic nitrogen compounds in the total absence of light. *Nitrosomonas*, for example, can do this. The energy needed for manufacturing the protoplasm of this species is obtained by the oxidation of ammonium compounds to nitrites. This reaction, just as any oxidation, releases considerable energy.

$$2\,NH_4OH + 3\,O_2 \longrightarrow 2\,HNO_2 + 4\,H_2O + \text{energy}$$

It is possible that among some protozoan species, the energy produced by oxidation of ammonia may supply part of that needed for the production of carbohydrates from carbon dioxide and water.

This process for producing organic substances is referred to as *chemosynthesis*, in contrast to *photosynthesis*, which depends upon the presence of chlorophyll and the action of light upon it in the presence of carbon dioxide and water. Photosynthesis is far more common than chemosynthesis in nature.

Many animals have colored substances (pigments) in their epidermal layers. Light usually results in the contraction of the cells containing pigments, but if the light is colored, the cells containing the corresponding color expand. Many reptiles, amphibians, fishes, and crustaceans have such pigment-containing cells, which are called *chromatophores*. More often than not, the pigment is black (melanin) and the chromatophore containing it is called a *melanophore*. Apparently, chromatophores function in aiding the animal to mimic its background by a process called protective coloration. As indicated in Figure 8, if the frog, or other animal with

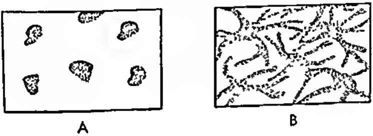


FIGURE 8

Sketch of chromatophores (melanophores) in the skin of a frog In A they are contracted, hence the skin is only lightly shaded In B the same cells have expanded, giving the skin a much darker appearance

melanophores, is placed against a light background, the melanophores contract, if the animal is placed against a dark background, they expand and the pigment flows out into the pseudopod like (see discussion of amoeboid movement, page 46) structures giving the animal a much darker appearance.

Any other behavior that animals may show on exposure to light depends upon the nature of the light. If the light is too intense, the animal may attempt to avoid it, if it is of low intensity, the animal may seek it This type of response is called phototropism If movement is toward the light, the animal is said to display a positive phototropic response, if movement is away from the light source, the phototropic response is negative.

Relation of Pressure to Living Substance

Increase in atmospheric pressure does not affect living plants or animals greatly until it becomes marked Yeast cells and many bacteria can withstand pressures of 600 to 1000 atmospheres, many protozoans, up to 800 atmospheres Decreasing the pressure below atmospheric has little effect, if the oxygen tension is kept constant The effects of pressure are discussed further in Chapter 29

Relation of Chemicals to Living Substance

Of the tremendous number of chemicals—oxygen, carbon dioxide, calcium, sodium, potassium iron, and so on—those of greatest importance to life functions will be considered Oxygen and carbon dioxide are treated in Chapter 30, and this discussion will therefore be limited to other more important types of chemicals

Usually, when one refers to the environment he is referring to the external environment—the air, the earth, and other forms and structures that surround humans and other animals The integument or covering which surrounds the bodies of animals and the functions carried out by certain mechanisms closely associated with the integument guard against the dangers of rather great environmental changes The environment that primarily concerns the body cells is the *internal environment*, which immediately surrounds them This internal environment is the tissue fluid Lower animals, such as protozoans, sponges, and coelenterates, have no internal environment, and their cells are therefore exposed to the full force of external environmental changes

It is interesting to note that the types of salts and their concentrations in the body fluids of many animals are very nearly the same as those of sea water, in higher vertebrates, however, the salt concentration of the blood is lower than that of sea water Ringer realized years ago (1874) that salts were essential in the body fluids He devised a solution containing proper quantities of calcium, sodium, and potassium with which he could perfuse an animal heart and cause it to continue beating for many hours so that he could study the heart action This solution is used extensively in the laboratory for bathing tissues to keep them alive for study purposes and is known as Ringer's solution

It is almost certain that all protoplasm requires some calcium (only a trace in some cases), as well as potassium and sodium These elements in the form of ions are extremely important in many physiological processes and are considered from time to time in later chapters

ENZYMES AND ENZYME ACTION

Enzymes accelerate chemical reactions The two chief types of reactions that occur in living substance are (1) *hydrolysis* and its reverse process *dehydration*, and (2) *oxidation* and its reverse process, *reduction* Hydrolysis is the common type of reaction found in the digestion of foods For example, when double sugars, such as cane sugar, are broken down

to simple sugars, such as glucose, in the intestinal tract, a molecule of water reacts with each molecule of double sugar broken down

$$C_{12}H_{22}O_{11} + H_2O \longrightarrow 2\ C_6H_{12}O_6$$

This is a hydrolytic process

An example of an oxidation process as it occurs within living cells is the breakdown of glucose to carbon dioxide and water, which is accompanied by release of energy This oxidation may be illustrated in the following manner

$$C_6H_{12}O_6 + 6\ O_2 \longrightarrow 6\ CO_2 + 6\ H_2O + \text{energy}$$

This equation represents the ultimate reaction—that between glucose and oxygen to produce water, carbon dioxide, and energy for work or maintenance of body temperature Actually many intermediary reactions occur each of which requires at least one enzyme (in many cases more than one) for its completion

These reactions (hydrolysis or oxidation) could not be carried out in vitro (outside the body), without the aid of very concentrated acids or high temperatures, that is, acids much more concentrated or temperatures much higher than the body could stand Numerous enzymes, however, accelerate these reactions within living protoplasm As pointed out previously, these agents act in the same way as do inorganic catalysts and are soluble in water.

All the enzymes thus far isolated have been identified as proteins None has been produced in the laboratory except by living cells Their specificity is usually limited to group specificity For example, *proteolytic enzymes* attack all proteins and break them down to simpler substances, *amylases* affect starches

Enzymes may be defined as *water soluble, colloidal organic catalysts more or less specific in action produced by living cells and destroyed by heat* Enzymes are believed to be essential to every living process and enzyme action enables living substance to produce more of itself and grow

ADDITIONAL READING

Davson H , *Textbook of General Physiology* (Blakiston, 1951), chs 7, 8 Osmosis, membrane permeability

Rogers C G , *Textbook of Comparative Physiology* 2nd ed (McGraw Hill 1938), chs 2 3 6 Solutions membranes phenomena of life

2

The Organization of Animals

All living cells are surrounded by a fluid medium and it is known that many physical and chemical processes that occur within this fluid medium affect the cell in some way or other Within limits living cells can adjust themselves to changes in their environment Moreover some although not all can even modify their environment for example certain protozoan cells when placed in a culture solution at a *p*H level unsuitable for their maximum growth are able to change the *p*H to a more favorable value The ability to do this is very limited and if the animal cannot adjust itself it dies or at least leads a very abnormal life The adjustive capacity of cells of higher animals is even more limited than those of lower forms

The functions of the fluid media of living cells are discussed in more detail in Chapter 20 however, it should be understood that the cells of all higher animals as they develop to form tissues and organs are at all times suspended in a nutritive fluid medium

DEVELOPMENT OF CELLS

The study of the development of animals is covered in the field of embryology Mere mention will be made of some of the changes of physiological interest that take place during development

The protozoan cell is a complete organism It has no specialties all of its living functions being carried out on approximately equal levels Protozoa do have parts of their cells specialized for example the cilia which cover the surface of *Paramecium* and cause it to move by their whiplike strokes the food vacuole of the amoeba which is only a temporary structure and the stalk of *Vorticella* which is specialized for contraction These are only parts of cells and therefore not made up of cells or tissues as are organs of higher forms they are sometimes called *organelles* Division of labor does exist then in the unicellular forms but the division is within the cell itself

In metazoan forms (see phyla in Figure 9) a division of labor prevails throughout the bodies of organisms The various tissues are distinguishable from one another by their specializations That is a muscle cell contracts a nerve cell conducts and a gland cell secretes each doing its work

for its own benefit as well as for the benefit of most other body cells Al though each such specialized cell still carries on all the living processes mentioned previously, it has become so modified that it performs one or two functions exceptionally well

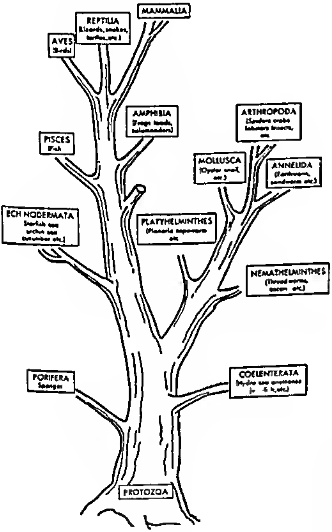


FIGURE 9

The evolutionary tree of an mals Only the most impor tant phyla of the animal kingdom and the vertebrate classes are given

In the following pages it will be seen how these cells become associated in formation of tissues and how with further organization they may be come specific structural and functional systems in such a complex organiza tion as the human body

MITOSIS

Three types of division are known to occur in the cells of plants and animals *fission* *meiosis* and *mitosis* Fission is a mere pinching in two of the nucleus and cell and is not as common as it was once thought to

be Meiosis, the type of division that occurs in germ cells when they produce spermatozoa or ova, is discussed in connection with reproduction in Chapter 40 At this point a discussion will be given on development of the individual after the spermatozoan has united with the ovum up to the time when tissues and organs are produced

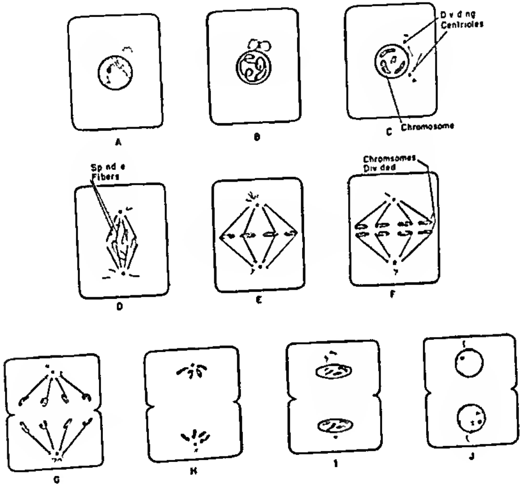
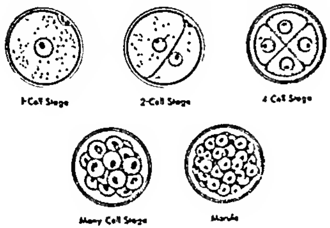


FIGURE 10

Mitosis or indirect cell division A B C and D prophase E and F metaphase G and H anaphase I and J telophase The chromosomes (C) line up in equatorial plate formation (E and F) soon after the nuclear membrane breaks down The chromosomes then divide equally (they can reproduce themselves) and pass to the two poles of the cell where a new nuclear membrane is formed as the cell itself divides

Mitosis, the most common form of division begins soon after fertilization when the egg divides into two daughter cells which in turn divide into four, and so on Mitosis or indirect division (Figure 10) from the Greek word *mitos*, meaning **thread**, refers to the fact that the chromatin

material collects into a threadlike structure before division takes place. These chromatin threads form the chromosomes which can reproduce themselves and then divide into two groups after which the cell divides. In man, cell division proceeds until finally there is a small, solid mass,



TISSUES

As the embryo continues to develop, each germ layer begins formation of the tissues for which it is specialized. The ectoderm produces skin and the glands connected with it, hair, salivary glands, mucous glands of the mouth and nose, enamel of the teeth, and the nervous system. The endoderm forms the epithelium of the digestive tract, the digestive glands, lungs and respiratory passages, and epithelium of the urinary bladder, urethra, and thyroid gland. From the mesoderm arise smooth and striated muscles, the skeleton, all but the enamel of the teeth, all but the epithelial lining of the digestive tract, the heart, blood vessels, lymph vessels and nodes, the blood, reproductive organs, kidneys, ligaments, tendons, and the lining of the body cavities.

A *tissue* may be defined as a group of cells, all of which have the same origin, structure, and function. The many tissues in the bodies of higher animals may be placed into four general groups: epithelial, supporting, muscular, and nervous.

Epithelial tissues cover body surfaces and function in secretion, absorption, and protection. Those covering the outside of the body and lining

FIGURE 13

Epithelial cells. A, simple squamous epithelial cells from skin surface; B, ciliated columnar epithelial cells similar to those found in trachea and Fallopian tubes.

the internal structures (alimentary tract, trachea, and so on), which have ready access to the outside are the true epithelial tissues. Those that line blood and lymph vessels are *endothelial tissues*. The glands of the body consist of epithelial cells. Those glands that have cavities and secrete their products by way of ducts are called *exocrine* glands, in contrast to the ductless or *endocrine* glands that secrete directly into the blood stream. The exocrine glands may be either *tubular* (simple or compound) or *saccular* (simple or compound), as illustrated in Figure 14.

Connective tissues function in strengthening and connecting various structures; the two most important types are (1) *white fibrous* tissue and (2) *yellow fibrous elastic tissue*. *Supporting tissues* include cartilage and bone tissues and usually have comparatively few cells but a large amount

of *intercellular substance* or *matrix.* They are also classified under connective tissue.

Cartilage cells lie in spaces within the matrix or intercellular substance, which are called *lacunae.* Cartilage may be *temporary* or *permanent.*

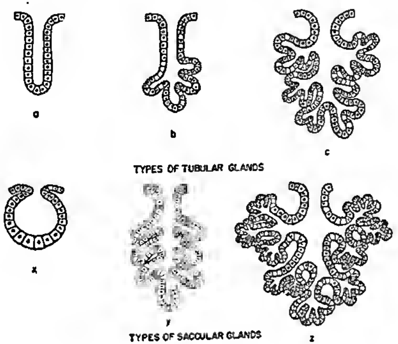


FIGURE 14

Tubular (a, b, c) and saccular (x, y, z) types of glands. The cells are epithelial.

Most of the cartilaginous structures that are found in the body before birth become bone in later life. Some cartilage, on the other hand, remains *permanent* throughout life; although it may become *calcified*, it does not take on bony characteristics—the calcium salts are merely deposited in the cartilage. Such deposits may be a factor in the stiffness of old age, since the calcified condition is certainly not conducive to active movement.

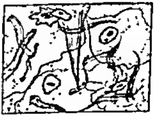


FIGURE 15

Sketch of connective tissue from subcutaneous region

Three types of cartilage are found in the bodies of animals:

1. *Hyaline cartilage* (Figure 16) makes up all the temporary variety as well as some of the permanent. Examples of permanent hyaline cartilage are the rib cartilages, the cartilage of the nose, and the cartilage found in the rings of the windpipe.

2. *Fibrous cartilage* is found in many structures such as the discs between the vertebrae (intervertebral discs), the cartilage of the knee joint, and the cartilage of the lower jaw.

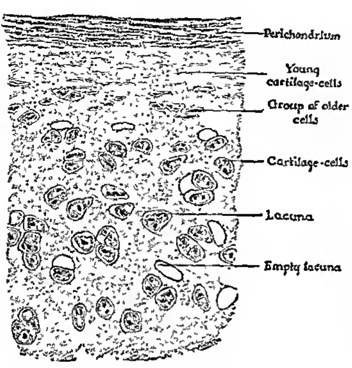


FIGURE 16

Hyaline cartilage, showing cells in lacunae or spaces (From Greisheimer, *Physiology and Anatomy*, by permission of J. B. Lippincott Company.)

3. *Elastic cartilage* contains a large number of elastic connective tissue fibers in its matrix. It has a yellowish color and is found in the external ear (pinna and canal), parts of the larynx, and the epiglottis. Muscular and nervous tissues will be studied as such in the chapters concerned with muscular movement and conduction.

BONE

Bone consists of both organic and inorganic material; about two thirds of its dry weight is inorganic. The organic portion consists chiefly of a protein (*ossein*), which, when boiled, yields gelatin. The inorganic portion of bone is chiefly calcium phosphate, $Ca_3(PO_4)_2$, but it also contains rather large quantities of calcium carbonate, $CaCO_3$. Vitamin D plays a very important role in the normal deposition of these calcium salts. It is well known that *rickets*, a calcium and phosphorus deficient condition of bone, may appear in children whose diets are inadequate in Vitamin D content or who are not sufficiently exposed to sunlight, which acts on certain substances beneath the skin to produce vitamin D.

Microscopic Structure of Bone

Bone may be classified according to the manner in which it is produced For example, some bone is formed by the action of bone forming cells, *osteoblasts*, which deposit the protein material and calcium phosphate upon a matrix consisting of connective tissue Because of the membranous nature of the connective tissue, this type of bone is referred to as *membrane bone* The other type is *cartilage bone*, which is formed and deposited by the action of osteoblasts on hyaline cartilage

Eventually the osteoblasts become surrounded by the solid material which they have produced and the bone takes on its characteristic microscopic appearance (Figure 17) The cells are contained in cavities called *lacunae* *Haversian canals* are tubelike structures surrounded by concentric layers of bone They contain blood vessels that carry materials to the bone forming cells

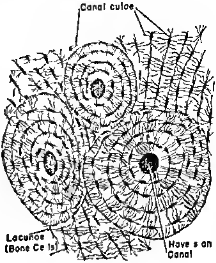


FIGURE 17

Microscopic structure of bone

SYSTEMS OF THE BODY

Tissues within the bodies of animals develop to form organs and the organs form systems, each of which is concerned with carrying out vital functions In the bodies of mammals nine systems may easily be identified (1) the *skeletal system*, which, primarily lends support and provides the main body framework but also serves as a storage place for many materials (calcium, iron and certain metals which would be extremely toxic if free in the body) and is the place of origin of many cells found within the blood (2) the *muscular system* which is concerned with movements of the skeletal framework of the body (3) the *nervous system* which coordinates the activity of nearly all of the other organs and tissues (4) the *circulatory system*, through which oxygen nutrients and products resulting from metabolism are transported from one region of the body to another (5) the *respiratory system* which together with the circulatory system brings oxygen into the body and removes carbon dioxide (6) the *digestive system* which affects the breakdown (digestion) of food that must precede its absorption into the blood stream for transport to cells of

the body and later used, (7) the *excretory system*, which is concerned with ridding the body of waste products of metabolism, (8) the *endocrine system*, the glandular organs of which maintain the delicately balanced function of cells and tissues Actually, the endocrine glands make up the second great coordinating system of the body, but generally the effects appear rather slowly and are of longer duration than in the case of changes caused by the nervous system, (9) the *reproductive system*, which is concerned with production of ova or sperm and, in the female, with furnishing essential nutritional conditions during the prenatal life of the newly formed individual

Each of these systems is considered in detail in a later chapter The skeletal system is treated first because of its importance in determining structural organization of the vertebrate body

ADDITIONAL READING

Maximow, A A, and W Bloom, *A Textbook of Histology*, 5th ed (Saunders 1948), chs 2, 4 7 Epithelial and connective tissue, bone

Part Two

STRUCTURE and MOVEMENT

3

The Skeleton of Animals

The skeleton of animals serves in a supporting and a protective capacity The more primitive type of skeleton is the *exoskeleton* with external supporting structures If we include all structures of a supporting and protective nature under the term skeleton some of the protozoans may be said

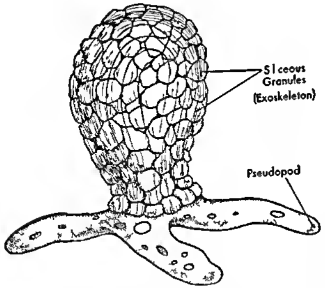


FIGURE 18

Difflugia an amoeboid protozoan that builds its own exoskeleton (shell) from minute sand particles

to possess skeletons These simple exoskeletons are usually external coverings in the form of shells calcareous (mainly calcium carbonate) or siliceous (composed of silicon) which are chiefly protective in function (Figure 18) The most common type of exoskeleton is that of the arthropods (insects crabs and related forms) This is made up of a substance called *chitin* a polysaccharide similar to cellulose but containing some nitrogen in its molecule Because the hard shell limits the extent to which the animal may grow the chitinous exoskeleton is shed periodically by a molting process called *ecdysis* The delicate animal then takes in large volumes of water so that its body becomes swollen and a new exoskeleton is formed as a result of secretions of the outer skin surface Thus by repetition of this process the animal is able to continue to increase its

size (Figure 19) Among the vertebrates fish have a scaly exoskeleton and the shell of the turtle is also a well known example of the latter

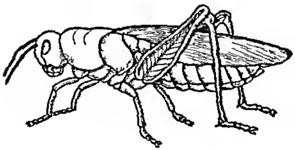


FIGURE 19

A grasshopper an animal encased in a chitinous exoskeleton

However if an animal were to attain a great size, this heavy external armor would become unwieldy The development of an *endoskeleton* with internal supporting structures furnishes a light flexible framework of sufficient strength to support the enormous weight of some of the largest land animals known to man—the modern elephant or the extinct dinosaur for example Man has an exoskeleton in the form of nails hair and teeth but his body is supported by a well developed *endoskeleton*

The scattered siliceous spicules of the sponge are difficult to classify but should probably be listed as parts of an endoskeleton since they function in supporting the organism (Figure 20) However a true bony

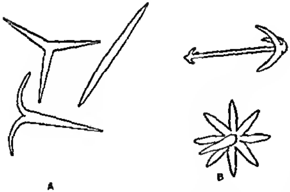


FIGURE 20

Spicules which make up the skeletal framework of some sponges A calcareous spicules B siliceous spicules

endoskeleton is developed in the vertebrates its structures being formed from portions of the mesoderm Deposition of insoluble calcium salts gives rigidity to bone but in all cases living cells continue to be active and a blood lymph and nerve supply is maintained within the bone In addition ligaments and tendons attach the bones to one another

The most primitive portion of the endoskeleton is the *notochord* This is a rodlike structure extending lengthwise through the dorsal regions of the bodies of *vertebrate animals* In the elasmobranch fishes (sharks for example) the notochord and the skull are composed of *cartilage* In higher

fishes and all other vertebrates, the notochord is found only in embryonic forms and gives way to a segmentation and inclusion of a bony structure with the appearance of a back bone The fins of fishes are the fore runners of the appendages of land animals Eventually these become spe cialized for supporting the animal for land movement and finally they reach a state of differentiation for efficient rapid movements of the ele vated body over land (legs) and for grasping objects (hands)

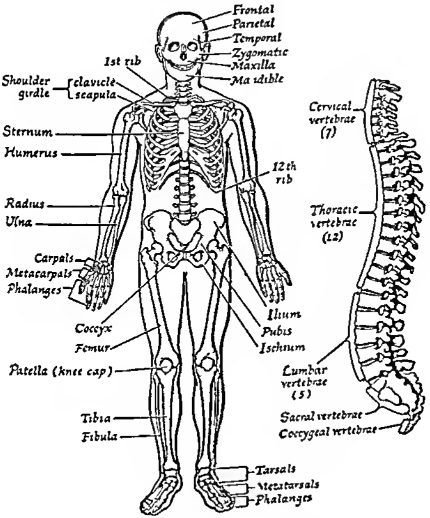


FIGURE 21

The human skeleton (From Pauli *The World of Life* by permission of the Houghton Mifflin Co)

THE ENDOSKELETON OF MAN

We recognize an excellent example of the high degree of efficiency which may be attained by the endoskeleton when we consider its development in

the human body However homologous structures are seen for most skeletal structures in other vertebrates

The Axial Skeleton

The human skeleton is divided into the *axial skeleton* consisting of the bones of the skull and trunk The bones of the skull which make up the cranium enclose the brain and protect it The bones of the face support

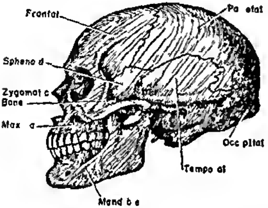


FIGURE 22

S de view of human skull

or lend protection to the eyes nose and buccal (mouth) cavity and the jaws function in tearing and chewing as well as aiding in the production of sounds created by different animals

The *vertebral column* is made up of thirty three bones seven *cervical* twelve *thoracic* or *dorsal* five *lumbar* five *sacral* (united to form the sacrum in adults) and four *coccygeal* vertebrae These vertebrae are constructed and arranged in such a manner as to allow considerable movement of the trunk which would be impossible if the column were simply a straight rigid tube A cartilaginous pad between the bodies of the vertebrae further facilitates their movement The spinal cord passes through the spinal foramina and the spinal nerves pass out through the openings on each side of the vertebrae (the intervertebral foramina)

The twelve *ribs* articulate (form movable joints) dorsally with the bodies of the thoracic vertebrae and their transverse processes ventrally the ten upper pairs are attached to the sternum or breastbone by means of the costal (rib) cartilages The two lower pairs are called *free* or *floating ribs* The sternum consists of three parts the manubrium at the top, the body and the ensiform cartilage or xyphoid process

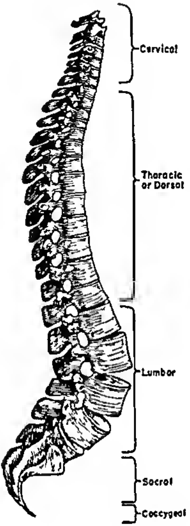


FIGURE 23

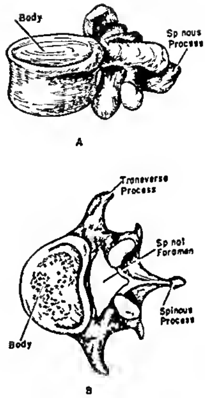


FIGURE 24

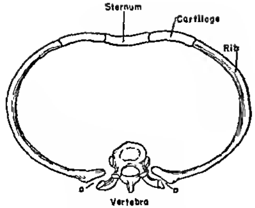


FIGURE 25

Indicating diagrammatically the way in which the ribs articulate (a) with the vertebrae

radius and *ulna* of the wrist the *carpals* of the hand proper, the *metacarpals*, and of the fingers the *phalanges*

In the adult the pelvic girdle consists of a large rigidly fixed bone on either side, the *os innominatum* In children each innominate bone is found to be divided into three parts —the *ilium* the *ischium* and the *pubis* During development these bones gradually interlock firmly with the formation of a deep socket at the point where they meet The head of the long bone of the upper leg the *femur*, fits into this socket The lower leg bones are the *tibia* (shin bone) and the *fibula* which is the small bone of the calf The *patella* (kneecap) lies in front of the lower part of the femur and articulates with it The bones of the ankle and arch of the foot are the *tarsals* (comparable to the carpals of the hand) and *metatarsals* The bones of the toes like those of the fingers are called *phalanges*

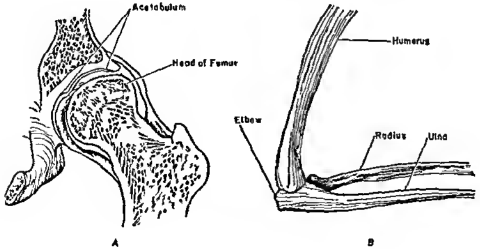
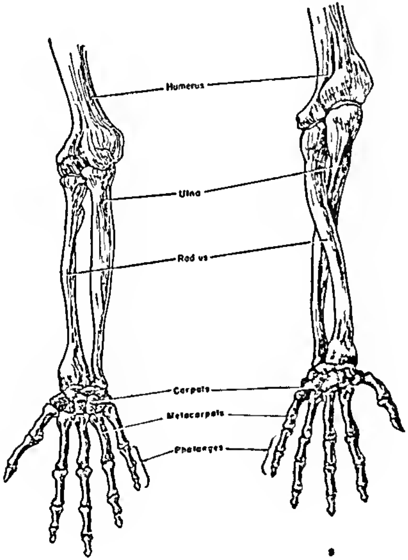


FIGURE 26

A ball and socket joint at hip B hinge joint at elbow

Articulations

The points at which bones make contact or unite with one another are called *articulations*. There are three types: (1) those articulations in which the bones are firmly united so that no movement takes place between them, such as occur in the *sutures* of the skull, (2) those in which the bones are joined by cartilaginous discs (the bodies of the vertebrae or the two pubic bones which form the pubis) or by ligaments (the lower articulation of the tibia and fibula) so that there may be some degree of



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movement, and (3) the true joints, which allow for considerable movement

The true joints comprise several types a few of which we may consider here The *ball and socket* joint is typified by that occurring in the hip (pelvic girdle), into which the head of the femur fits, and by that occurring in the shoulder girdle into which the humerus fits At the point of articulation, the bones are covered with *cartilage*, which in turn is covered with a *synovial* membrane The latter forms a saclike structure within which it secretes a lubricating fluid called *synovial fluid* There are many *hinge joints* in the body, of which those of the elbow, the fingers and the knee are examples In this type, also, cartilage and synovial membranes appear at the point of articulation The *pivot joint* may be illustrated by the bones of the forearm the radius and ulna, these bones are so formed and arranged that the radius can rotate about the ulna, which acts as the pivot *Gliding joints* are found in the carpal bones of the wrist and the tarsals of the foot Although the movements of these bones are not great, they can slide one over another to some extent

The skeletal and muscular systems are closely associated in their functions for furthering movement of the body The bones of the skeleton form levers which are controlled by muscles attached to them The function of these levers is discussed in Chapter 5

ADDITIONAL READING

Gray H *Anatomy of the Human Body* 25th ed (Philadelphia Lea and Febiger 1948) pp 59–252 255–338 Skeletal structures articulations

4

Classification of Movement

MOVEMENT is a property of all matter, but is most strikingly manifested in living substance In fact, so pronounced is this property that it is often used to determine whether or not a piece of matter is living Although there was for many years a tendency to distinguish plants from animals by the movement or locomotion (movement from place to place) of the latter, it is now known that plants or some of their structures are also capable of both movement and locomotion Protoplasm may evidence a number of types of movement *molecular* (as evidenced by Brownian movement), *streaming amoeboid, ciliary*, and *contractile*

MOLECULAR MOVEMENT

Molecular movement is a physical property of all matter, but it is usually considered in terms of inorganic matter, especially gases Everyone has observed the movement of gas molecules in the gradual dispersion of a smoke cloud as it comes from the stack of a locomotive or from the chimney of a house Such dispersal (diffusion) would occur even if there were no air currents in the environment because of the constant movements of

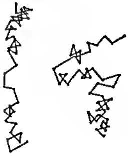


FIGURE 28

Camera lucida tracings of the movements of two different protoplasmic particles as seen under the oil immersion lens of the microscope The movement is referred to as *Brownian movement* and is caused by molecular bombardment

molecules themselves Although the molecular movement cannot be seen even with the aid of a microscope evidence of such movement is visible under high magnification of the microscope in the movement of larger, but still microscopic particles The movement of these particles, called *Brownian movement* after the investigator who first noticed it, is owing

to the collision of molecules with larger particles in solution and may be seen in living or nonliving material provided that the dispersion medium is not too viscous Figure 28 shows a tracing, made by means of a camera lucida, of the movements of such particles Note how irregular and zigzag their movements are Brownian movement occurs only in solated (fluid) protoplasm, gelated (viscous) protoplasm is too rigid a medium

STREAMING MOVEMENT

Protoplasm is not necessarily quiescent but may be in constant movement Streaming movements may be observed in the protoplasm of many plant and animal cells Biologists believe that active streaming movements occur, at least at times, in most if not all, living protoplasm which, therefore, is not the inert substance it appears to be in many cells If a thin slice of an *Elodea* leaf, for example, is placed under the microscope, streaming movements may be observed quite readily This phenomenon

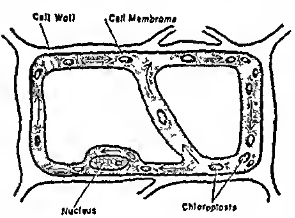


FIGURE 29

Sketch of a cell from the water plant *Elodea* The arrows indicate the direction of protoplasmic streaming

is not so common in animal as in plant cells although in paramecium (one of the protozoa) food vacuoles and other structures can be seen flowing slowly in a clockwise direction within the organism This phenomenon, known as *cyclosis*, may be observed also in other ciliated protozoa The fundamental cause of streaming remains obscure, although many theories have been advanced in an attempt to explain it, the majority of which however are rather fantastic and need not be discussed here The most acceptable theory suggests that movement is caused by alternating gel sol changes in the protoplasm, such as occur in amoeboid cells

AMOEBOID MOVEMENT AND LOCOMOTION

Amoeboid movement in cells is owing in part to streaming movement within the protoplasm which may result in the formation of pseudopods

which may engulf food organisms by surrounding them or which may lead to movement of the cell itself from place to place (a process called locomotion) The name amoeboid movement was suggested because the movement occurs typically in common amoeboid forms such as *Amoeba proteus*, but cells that move in this manner are found in all classes of organisms

Occurrence of Amoeboid Cells

Practically all members of the class *Rhizopoda* (the class to which the amoebae are assigned) of the Phylum *Protozoa* depend upon the amoeboid form of movement Sponges (Phylum *Porifera*) possess wandering cells that move around in an amoeboid fashion In fact it was shown years ago that after the cells of a sponge are separated by forcing it through a sieve most of these cells assume an amoeboid habit and may move about until they again make contact with one another The sponge also produces eggs which are amoeboid

The hydra jellyfish sea anemones and so forth (Phylum *Coelenterata*) also have wandering cells that are amoeboid in their movement In the flatworms (Phylum *Platyhelminthes*) amoeboid cells are found in the alimentary tract and may function in the ingestion of food materials others are located in the mesoderm and may play a role in excretion

The threadworms (Phylum *Nemathelminthes*) have mesodermal cells that are amoeboid and may have some connection with excretory processes The spermatozoa of nematode worms are amoeboid (in most animals the spermatozoan is flagellated)

Amoeboid cells are found in the blood system tissue fluids lymph and other fluids of the body cavities of all other animals The most common of all are the leucocytes of the human blood stream and tissues which are discussed in Chapter 23

The Structure of Amoeboid Cells

Because of its size and the ease with which it can be cultured the species *Amoeba proteus* has served for most of the observations concerning amoeboid locomotion The streaming movement of the protoplasm its gelation at the anterior and its solation at the posterior end can be readily seen within this organism with the aid of a good compound microscope

Basically all amoeboid cells resemble those of *Amoeba proteus* in structure This unicellular animal consists of a central elongated fluid portion surrounded by a gelated mass The entire cell is enveloped by a thin elastic membrane approximately 0 -5 microns in thickness This membrane is called the *plasmalemma* the fluid part the *plasmasol* and the

gelated part, the *plasmagel*. Between the plasmalemma and plasmagel is found a clear layer (hyalin area), rather limited in thickness and difficult to see over most of the amoeba but usually more extensive at the tips of the

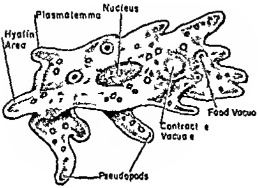


FIGURE 30

An amoeba with its various structures indicated

pseudopods where it is known as the hyalin cap. This hyalin area is quite fluid and variable in thickness.

If a motionless amoeba could be observed the plasmosol would have roughly the form of an elongated rod with an expanded anterior end. In the moving amoeba the plasmasol occupies the central portion of the cell and extends by flowing into the anterior portion. It contains many granules and crystals. The plasmagel, which is practically motionless even while the plasmasol is flowing, contains many granules and surrounds the plasmasol. The plasmagel is relatively rigid and resembles a tube through which the plasmasol flows. The portion at the anterior end of the cell which is very thin is referred to as the plasmagel sheet.

Amoeboid Cells and Application of Theories of Movement

The belief formerly held that amoeboid movement could be explained entirely on the basis of changes in surface tension is no longer accepted. Undoubtedly a lowering or raising of surface tension does affect living amoeboid cells to a limited extent, but this type of locomotion cannot be so simply explained. The theory of amoeboid locomotion suggested by Mast in 1926 seems to be most acceptable. It applies very well to most cells which show this type of movement. He concludes that four outstanding factors contribute to locomotion in amoebae and other amoeboid cells. These are (1) attachment to the substratum (bottom of culture dish or natural habitat), (2) gelation of plasmasol at the anterior end, (3) solation of plasmagel at the posterior end, and (4) contraction of the plasmagel at the posterior end. Gelation occurs at the anterior end and results in an extension of the tube through which flows the plasmasol that is formed at the posterior end.

The rate of locomotion in free living amoebae varies considerably (from approximately 1 0 to 4 5 microns per second) depending on the conditions of the environment Clearly, a true rate can only be obtained from mono

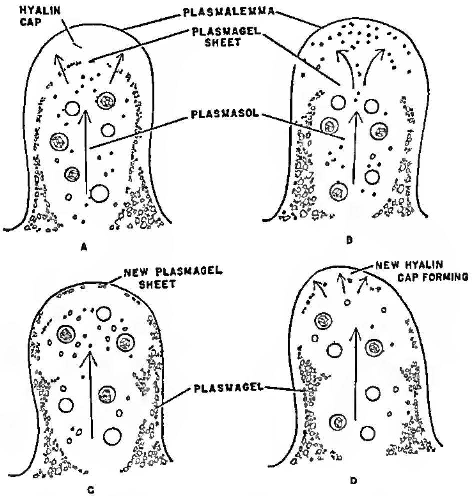


FIGURE 31

Sketches illustrating the various stages in amoeboid locomotion (after Mast) A diffusion through plasmagel sheet and formation of hyalin cap B rupture of plasmagel sheet and flow of plasmasol into hyalin cap C formation of new plasmagel sheet just inside membrane of pseudopod D diffusion through new sheet and formation of hyalin cap

podal forms Leucocytes on the other hand move much more slowly than amoebae and their movement usually is not visible except under optimum conditions In any event the speed of amoeboid locomotion is much less than that of streaming movements of plants and animals Within the amoeboid cells themselves the streaming movement is found to be several times as great as the forward movement or locomotion

Factors Affecting Amoeboid Locomotion

Amoeboid locomotion is affected by most of the common physical and chemical factors of the environment. The effects of changes in hydrogenion concentration and temperature are noticeable almost immediately. In *Amoeba proteus* too great a change from *p*H 6.8 (approximately) will slow movement. As the temperature is decreased from room temperature (approximately 21 degrees C.) movement decreases; an increase in temperature causes an increase in movement up to about 35 to 40 degrees C. at which point movement ceases. Alterations in oxygen, carbon dioxide, and salt content also influence locomotion, although the effects may not be so obvious until a longer period of time has elapsed. Naturally, oxygen is utilized in the production of the energy required for movement, but the production of energy for immediate use is not dependent upon the presence of oxygen. Locomotion can occur in the total absence of oxygen, a condition similar to that found in muscle and ciliated cells (such as in paramecia). Calcium, sodium, potassium, and magnesium salts are especially important in amoeboid movement, for they seem to play a role in the gelation and solation of protoplasm.

CILIARY MOVEMENT

Although Van Leeuwenhoek first observed ciliary movement about the middle of the seventeenth century, no serious consideration was given to this type of movement until cilia were discovered in the human body.

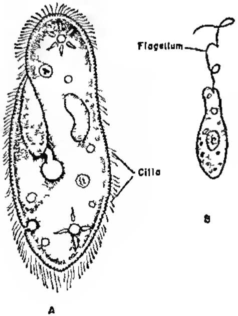


FIGURE 32

A *Paramecium*, a ciliated organism; B *Euglena*, a flagellated organism.

Cilia, which are hairlike projections, are found on some cells in animals of all phyla, with the possible exceptions of the Phyla *Nematoda* and *Arthropoda*. In some animal forms at least, cilia are only a part of the complicated mechanism that constitutes the "*neuromotor apparatus*," consisting of motor elements and conductile elements that control and coordinate the movements of cilia.

Flagella differ from cilia only quantitatively; that is, cilia are usually shorter and more numerous than flagella. The length, however, is not an absolute, rather, it is based on the size of the cell: the flagellum is usually longer than half the length of the cell, the cilia, shorter

OCCURRENCE AND FUNCTION OF CILIATED AND FLAGELLATED CELLS

Ciliated and flagellated cells are numerous and quite variable in the classes *Ciliata* and *Mastigophora* (Phylum *Protozoa*). Moreover, a "neuromotor apparatus" has been described in many forms In *Paramecium*, for example, such a mechanism is found, which consists of fibrils leading from a common center (neuromotor center) to the cilia. That

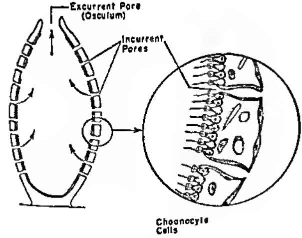


FIGURE 33

Sketch of a simple sponge, *Grantia*, with section enlarged to show flagellated choanocyte cells

these fibrils are probably conductile is indicated by the fact that when they are cut the coordinated beats of the cilia are interrupted

In the sponges are found many flagellated cells, which are called *choanocytes* because of the transparent collar like structure that surrounds the flagellum. Being incapable of movement from place to place, the sponge is dependent upon these cells for procuring its entire food and oxygen supply, and they also aid in excretion These cells line the canals and cavity of the sponge and beat in such a way that the water containing food and

oxygen is carried through the small pores of the sponge and on out through the osculum

Ciliated or flagellated cells are found, generally, among the *Coelenterata*. *Hydra*, a fresh water form, has numerous flagellated cells, which evidently serve the same purpose as the choanocyte cells of the sponge. The bodies of sea anemones are sometimes covered with ciliated cells

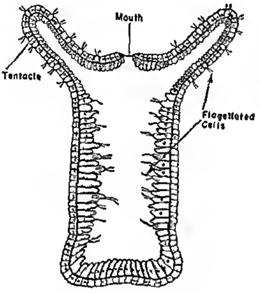


FIGURE 34

Illustrating flagellated cells in the fresh water coelenterate *Hydra*

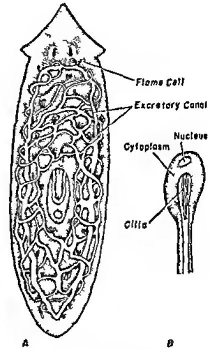


FIGURE 35

A, drawing of the flatworm *Planaria* to show the excretory system with 'flame' cells, *B*, enlarged view of a flame cell

The members of the Phylum *Ctenophora* have ciliated plates that have to do with locomotion

Some forms of *Platyhelminthes* are covered externally with cilia, which aid greatly in locomotion. Planarian flatworms, which live in fresh water, are of this type. Ciliated cells are also found in the excretory systems of flatworms and are referred to as flame cells because of their resemblance to a candle flame when in motion. These cilia force the excretory fluids through canals or tubes to the outside

The trocophore larvae of the *Annelida* are covered with cilia by means of which they carry on the process of locomotion. The adult worms have flame cells in their excretory systems.

Ciliated larvae of the *Echinodermata* and the lower *Chordata* are very similar. In the case of the starfish nearly every organ and every surface of the body is covered with cilia. Those on the surface keep it free of debris and cause currents that ensure a fresh supply of oxygenated water.

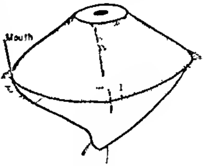


FIGURE 36

The ciliated larva of an annelid

The *Mollusca* are well known for the ciliated cells found on their gills. The cilia function in respiration and removal of debris.

Most of the species of the Phylum *Rotifera* depend upon cilia for movement. These organisms move from place to place attaching themselves temporarily to various objects in the environment. The cilia are also used in procuring food when the animal is attached. This act is accomplished by currents produced in the water by the cilia in such a way as to force small food particles toward the mouth.

In all the *Chordata* are found examples of ciliated or flagellated cells. Neither cilia nor flagella are utilized for locomotion of cells or organisms in fishes, reptiles, birds, and mammals with the following exceptions: the flagellated spermatozoa of animals and the young tadpole of the *Amphibia* which often moves by cilia both before and after it hatches from the egg. In these forms the cilia are used chiefly for movement of fluids and particles in the fluids.

In humans, ciliated cells are found on the mucous membranes of the nostrils, the nasal duct, and lachrymal sac. They also occur in the pharynx, Eustachian tube, and within the middle ear. Ciliated cells line the walls of the larynx, trachea, and bronchial tubes. In the bronchial tubes, ciliated movements cause the mucus to collect in a mass that may then be expelled during the coughing movements that follow. In the Fallopian tubes the cilia possibly function in the movement of the egg to the uterus. Within the *vasa efferentia* and the tube of the epididymis, ciliated cells aid in the passage of spermatozoa toward the seminal vesicles. The spermatozoa themselves, as mentioned above, are flagellated. On the walls of the ventricles of the brain, cilia probably function in increasing the move

ment of the cerebrospinal fluid. Ciliated cells also line the renal tubules of the kidney.

When the cilia or flagella of a cell strike the surrounding fluid they may function in one or both of the following ways: (1) they may move the cell itself, or (2) they may move the fluid surrounding it, that is, if the cell is unable to move or is normally stationary, only the water moves. Both movements have their advantages. In the first case, the cell (or organism)

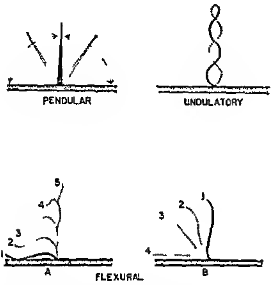


FIGURE 37

Sketches illustrating the three general types of ciliary or flagellar movement: pendular, undulatory, and flexural. *A*, *return stroke*; *B*, *effective stroke*.

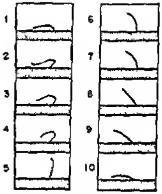


FIGURE 38

Copy of a series of moving pictures of the flexural type of ciliary movement. Successive positions are numbered from 1 to 10.

may be carried from place to place, thereby reaching food material and oxygenated water, whereas in the second case, the movements bring the food and oxygenated water to the cell.

CONTRACTILE MOVEMENT

Contractile movement is a property of most protoplasms, if not all; investigation has shown that even the lowest protozoan cell may show contraction of the protoplasm, although the contraction is not a specialized

function of the cell On the other hand, certain protozoan forms such as *Stentor*, *Vorticella*, and *Spirostomum* do show a specialized type of contraction Fibrils have been observed in these forms and are thought to be the true contractile elements responsible for contractile movement in these species They are called *myonemes* In Figure 39 is shown the structure of a portion of the stalk and the body of *Vorticella* This organism is capable of very rapid and strong contractions during which its fibrils or myonemes take on a spiral form

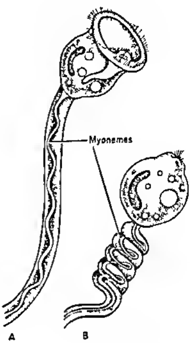


FIGURE 39

Myonemes in *Vorticella* A when animal is extended B when contracted

In all probability the fundamental processes involved in streaming amoeboid and ciliary movements are also involved in contractile movements Undoubtedly considerable information pertinent to a greater understanding of contractile movements could be obtained by observations that could be made upon some of these lower forms of animals For studying phenomena connected with muscle contraction higher forms of invertebrate and vertebrate animals are used

FUNCTIONS OF STRIATED CARDIAC AND SMOOTH MUSCLE

The functions of muscle in animals and man are many Striated muscles function in the movement of different skeletal parts and in posture The striated muscles of the larynx, diaphragm, ribs, and abdomen play a part in movements concerned with respiration, those of the jaws, tongue, cheeks, and upper part of the esophagus aid in the chewing and mixing of food in preparation for digestion, and those of the external anal sphincter aid in the expulsion of fecal matter, in urination or micturition the striated muscle of the external urethral sphincter plays a part, heat regulation during exposure to cold environment depends upon the shivering movements of striated muscles, which produce heat, striated muscles also take part in proper functioning of certain sense organs, such as the eye and the ear

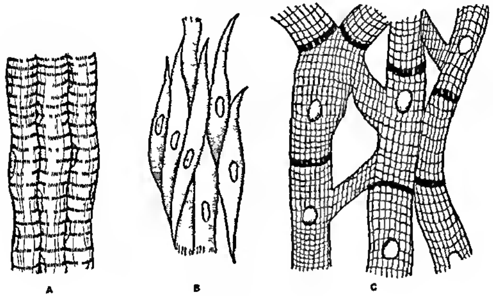


FIGURE 40

Types of muscle tissue found in mammals A striated or skeletal B smooth or visceral C cardiac or heart muscle

Cardiac muscle, as is well known, functions in the circulation of the blood, its contractions cause the pumping activity of the heart

Smooth muscles have many functions to perform in the viscera and other parts of the body Necessary to the circulation of the blood and lymph, they are also important in the regulation of blood pressure, for the smaller blood vessels are constricted or dilated by the contraction or relaxation of smooth muscles in their walls Respiration may be carried on with ease or difficulty depending upon the dilation (relaxation of smooth muscles) or constriction (contraction of smooth muscles) respectively, of the bronchioles

The smooth muscles of the lower part of the esophagus the stomach in testines and gall bladder are concerned with digestion absorption and excretion The smooth muscles of the ureter and bladder aid in urina tion those of the Fallopian tubes uterus *vas deferens* seminal glands and erectile tissue have to do with reproduction The smooth muscles attached to the base of hairs aid in heat regulation because the dead air space which acts as insulation is increased when the hairs stand erect Although of lit tle consequence in maintenance of human body heat this insulation is of great importance to lower animals

DEVELOPMENT OF CONTRACTILE TISSUE

Further discussion on the characteristics of the three forms of muscle will be made later but first of all it would be of value to understand the develop ment of contractile tissue from the more primitive to the more specialized that is from the ordinary primitive smooth muscle cell to the highly devel oped striated cell This extremely interesting development can be fol lowed by comparing these tissues as they occur in organisms of the different animal phyla

Although the *Porifera* (sponges) can hardly be said to possess muscle cells in the strict sense the somewhat elongated cells arranged about the *osculum* can contract and relax albeit very slowly Single contractile cells also surround the incurrent pores of some sponges (Figure 33 page 51) If the osculum is stimulated it takes about seven minutes to close the open ing This time lapse indicates the primitiveness of the conduction and contraction in sponge protoplasm Nevertheless these cells may be the forerunners of the muscle cell despite their limited contractile powers In fact the structure of these contractile cells of sponges is similar to that of a smooth muscle cell

Among the *Coelenterata* several types of contractile cells are found In *Hydra* one of the lowliest of the coelenterates there is evidence of the existence of true though structurally and functionally primitive contrac tile cells The chief type of contractile cells found in this species are of ectodermal origin and serve simultaneously as protective receptor and effector cells that is since they are epithelial they have a pro tective function just as other epithelial cells they also receive stim uli and conduct the resulting impulses to the contractile portion of the cell They are called *musculo epithelial cells* In some of the higher coelenterates such as the sea anemones contractile cells of endodermal origin occur They also are epithelial but differ somewhat from those of *Hydra* in that each usually has a long process which is mainly conductile in

function, leading from the receptor portion of the cell to the contractile part. Other types of contractile cells having the appearance of smooth muscle cells, and even contractile cells that have become sufficiently dif-

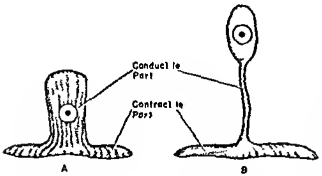


FIGURE 41

The musculo-epithelial cells of coelenterates. They are epithelial and conductile in nature at one end and contractile at the other end. A, an ectodermal cell. B, an endodermal cell.

ferentiated to acquire a slightly longitudinally striated appearance, also are found in coelenterates. The longitudinally striated cells of coelenterates, however, are not far advanced in complexity of structure over the primitive smooth muscle cell.

Among the flatworms, *Platyhelminthes*, there exists a smooth muscle type of contractile cell, which is somewhat similar to those found in the coelenterates.

In the *Nematoda* are found peculiar longitudinally striated contractile cells as well as smooth muscle cells, which are mesodermal in origin. This is the lowest Phylum in which muscle cells of mesodermal origin occur.

There is no evidence of cross striation occurring in muscle cells until the Phylum *Mollusca* is reached, where, in some of the species, cells resembling cardiac tissue are found. These cells show both cross and longitudinal striations. In some of the *Cephalopoda* are found muscle fibers that have diagonal striations. The diagonal appearance is evidently due to the spiral arrangement of the fibrils within the muscle cell or fiber.

The *Arthropoda* have both nonstriated and striated muscle cells all well differentiated and fairly similar to those found in the chordates. In fact the results of investigations carried out on insect muscles have added much to our understanding of the action of mammalian striated muscle.

Far more investigations on muscle contraction have been concerned with striated muscle than with any other. The greater part of the following discussion, therefore, will be taken up with this type.

5

Striated Muscle

STRUCTURE OF STRIATED MUSCLE

THE *voluntary striated muscle* of mammals and humans is so called because it commonly acts under conscious control and because of the bandings or cross striations which characterize the microscopic structure of the muscle fibers The muscle fiber or muscle cell, as stated previously, contains many nuclei and for this reason is called a syncytium The striated muscles are often referred to as skeletal muscles because they are attached to the bones

Striated muscle fibers are comparatively long, averaging 30 to 40 mm According to some authors, they may reach 30 cm, but this figure is questionable, since muscle cells can form long strands by uniting end to end, there is no need for such a great length The diameter of muscle fibers varies considerably, even in the same muscle, ranging from 10 to 100 μ The increase in size of a muscle as the result of exercise, work or the normal growth process, is owing to increase in diameter of individual fibers rather than to increase in fiber number

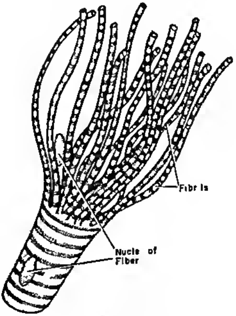


FIGURE 42

Striated muscle fiber torn open to expose fibrils

The skeletal muscle fiber or cell is made up of numerous longitudinal fibrils which may be aggregated into small bundles manifest in cross section As viewed in cross section the fibrils are referred to as the areas of Cohnheim The *sarcoplasm* (or muscle protoplasm) surrounds these fibrils The membrane of the fiber or cell enclosing the fibrils and sarcoplasm is called the *sarcolemma*

The muscle proper is made up of numbers of *fasciculi* (bundles of muscle fibers), bound together by connective tissue, and varying greatly in num

ber and in size Each fasciculus is surrounded by connective tissue (*perimysium*) and all the fasciculi forming the muscle are encased in a tough connective tissue sheath (*epimysium*)

Under normal conditions skeletal muscle is activated by its specific nerve if the nerve is cut, all voluntary movement ceases Skeletal muscle does not show automatic activity such as that exhibited by smooth muscle The skeletal muscle will contract only if it or its attached nerve is stimulated The fact that it responds to stimuli applied directly to it indicates that skeletal muscle shows *irritability* or *excitability*

INDEPENDENT IRRITABILITY OF MUSCLE

In the middle of the last century Claude Bernard proved very effectively by experiments with the drug curare that muscle possesses independent irritability

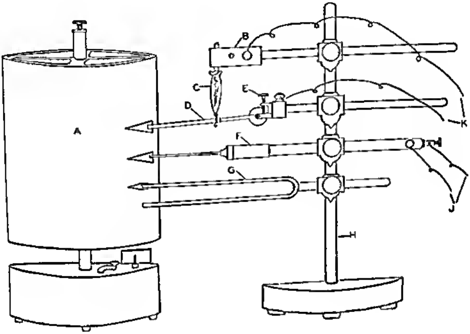
Curare is used by some tribes of South American Indians on the tips of their arrows The victims become paralyzed after injury by such arrows but the ability to experience sensations is not affected It is now known that the drug exerts its influence at the junction of the motor neuron (the nerve cell that leads to muscle) and muscle (myoneural junction) so that transmission of impulses across this junction is lost although the muscle fiber is not damaged that is the muscle responds after exposure to curare by direct stimulation only the impulses from its nerve having no effect Thus an animal or person poisoned with curare may experience pain and other sensations but may be unable to move

To demonstrate this in the laboratory the brain of a frog is destroyed Frogs and other cold blooded animals are useful for such experiments because their tissues will remain alive for hours and days after destruction of the brain Without cutting or injuring the sciatic nerve is dissected out in both thighs of the frog and carefully freed from the surrounding tissues A ligature (thread) is passed under the nerve and fairly tightly about the one leg In this manner the blood supply to that leg is cut off without interfering with nerve conduction Curare injected beneath the skin of the frog enters the blood stream and is carried to all parts of the body except the leg which is ligated After 15 to 20 min following the curare injection pinching the toe of the ligated leg is followed by contraction of the muscles of that leg there is no response to pinching in the nonligated leg If the sciatic nerve in each leg is stimulated electrically, the muscles of the ligated leg contract the muscles in the other leg do not If however the muscles in each leg are exposed and stimulated directly, a response is ob

tained in both cases Curare blocks the junction between the muscle and nerve (myoneural junction) so that no impulses reach the muscle by way of the nerve Yet the muscle responds to direct stimulation, proving that it is independently irritable

METHODS USED IN THE STUDY OF MUSCLE PHYSIOLOGY

There are two methods by means of which study can be made of the response of a muscle to stimulation (1) the *isometric method* in which the muscle is fastened in such a way that it cannot contract and most of the



of *Achilles*) is fastened to a muscle lever so that when the muscle is stimulated the lever is lifted through space With the proper arrangement and apparatus, numerous experiments can be performed that should give a fair knowledge of the behavior of muscle In fact, very little, if anything was known about the physiology of muscle until after the years 1846–1850 during which period the graphic method was first employed by Weber and Helmholtz This entailed the use of a *myograph* (now called the kymograph) by means of which tracings (myograms) of a muscular contraction can be obtained Records or myograms can be made on smoked paper on the revolving drum of a kymograph The myograms best suited for analysis are those obtained from muscles of *poikilotherms* (cold blooded animals), such as frogs, because the excitability of muscle and nerve in this group is of much longer duration than that in the *homoiotherms* (warm blooded animals)

STIMULATION OF MUSCLE

Although any one of several types of stimuli (mechanical, chemical thermal, or electrical) may be used to cause contraction, the type usually employed is electrical This latter method of stimulation is more desirable for several reasons (1) the ease of application, (2) the control of intensity, (3) the lack of severe damage to the tissue which may result from other methods of stimulation, and (4) the fact that the electrical stimulus is quite similar to the normal physiological excitation transmitted by the nerve The electrodes may either contact the nerve of a nerve muscle

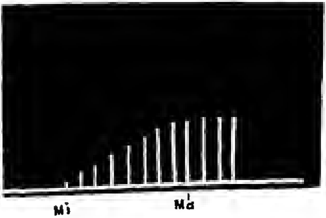


FIGURE 44

Kymograph record of minimal and maximal stimuli The intensity of the current at zero when the test was begun (the secondary coil of the inductorium was at its greatest distance from the primary coil) was increased progressively Only break shocks were used for stimulating The minimal stimulus was obtained when the secondary coil was at 13 cm from the primary—the muscle barely contracted (Mi) The maximal stimulus was at 4 cm (Ma)

preparation or contact the muscle directly The apparatus commonly used for obtaining the proper electrical stimulation is the inductorium (induction coil) With this apparatus the intensity, rate, and duration of stimuli can easily be controlled

When an electrical stimulus is applied to a muscle or to the nerve of a nerve muscle preparation, results show that by gradual, successive increases in intensity from zero (at which point no contraction is observed), an intensity is finally reached where a very feeble contraction occurs This is the *minimal stimulus* (also called *liminal* or *threshold stimulus*) A stimulus of less intensity is designated as *subminimal* If this intensity is further increased, a greater contraction of the muscle is obtained with each successive increase until a point is reached above which there is no further increase in contraction This is the *maximal stimulus*, and any stimulus or contraction between minimal and maximal is designated as *submaximal* (Figure 44) A more powerful stimulation beyond the point of maximal stimulus may cause destruction of the nerve or muscle

SIMPLE MUSCLE CONTRACTION

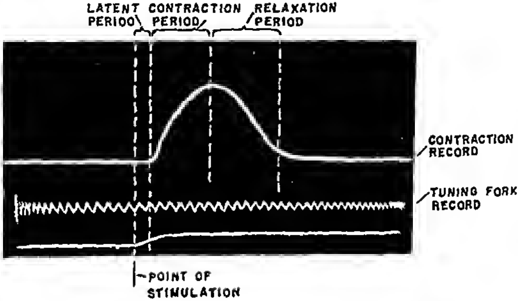
When a fresh muscle, prepared and fixed for isotonic contractions, is stimulated by a single maximal stimulus, the resulting contraction, followed instantly by a relaxation is termed a *simple, or single, muscle twitch* The latter is not the type of contraction usually occurring in human muscles during normal activity, but that resulting from a single volley of nerve impulses A record of a simple muscle twitch showing the movement of the muscle lever on a revolving drum is presented in Figure 45

An examination of this record reveals that the simple muscle contraction may be divided into three intervals the *latent period*, the *contraction period*, and the *period of relaxation*

The Latent and the Refractory Periods

The latent period is that interval following stimulation, when various mechanisms involved in final production of energy for the contraction of muscle are active, it varies in length of time according to the type of animal muscle, and apparatus used In the case of the frog gastrocnemius (the muscle of the lower leg), using the type of apparatus shown in Figure 43 the latent period is around 0 01 second The true latent period is much shorter than this, but artificial conditions have lengthened it If the muscle is stimulated through the nerve the latent period is much greater and will include the time it takes the impulse to travel down the nerve and cross the nerve muscle (or myoneural, or muscle end plate) junction Actually,

in view of results obtained with extremely delicate apparatus it appears that the time required for the muscle to initiate contraction after the stimulus has reached it, may be nearer to 0.004 sec., and that the time for changes associated with the development of tension, or response, in the protoplasm of the muscle is even less



of time required for the cells to recover from these changes is called the refractory period At the end of this interval, the muscle is again irritable

It is possible to distinguish two refractory phases (1) an *absolute refractory period*, at which time the strongest stimulus will fail to engender a response in muscle that has received an initial stimulus, and (2) a *relative refractory period*, when a second stimulus, if sufficiently stronger than the first, may elicit a response

In cardiac muscle the absolute refractory period begins immediately at the time of stimulation and lasts almost through the contraction phase, and the relative refractory period lasts throughout the relaxation period For this reason the heart muscle very seldom contracts a second time before it has completely relaxed Consequently, the long refractory period results in the rhythmical nature of the heartbeat and the heart cannot be thrown into complete *tetanus*

The Contraction Period

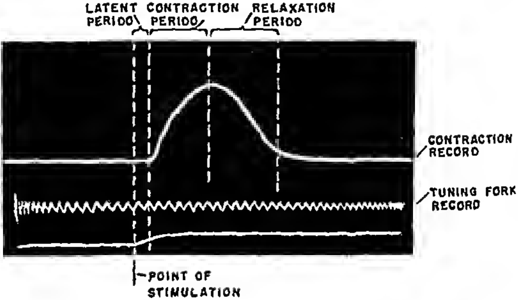
The *contraction* or *shortening* period follows immediately after the latent period, that is, when the tension of the muscle is sufficient to overcome its own inertia and that of attached objects such as lever, scale pan, and weights The time of each contraction varies considerably with different species, and in different muscles of the same species It is shortest in insects (0 001 and less in wing muscles), longer in birds, still longer in mammals, and longest of all in poikilotherms, other than arthropods In the frog gastrocnemius, it is about 0 04 to 0 05 sec

Numerous investigations have been made in an attempt to locate definitely where in the muscle cell the shortening or contraction begins, but as yet there seems to be no general agreement as to its location The dark bands of the fibrils increase in volume during contraction but it is not known whether they increase at the expense of the fluid sarcoplasm surrounding the fibrils or of the substance of the light bands within the fibrils

RELATIONSHIP OF STRIATED MUSCLES TO THE SKELETAL SYSTEM

The student has acquainted himself to some extent with the skeletal system and the arrangement of bones as discussed in Chapter 3 This knowledge is of considerable value when studying the work done by striated muscles These muscles usually consist of a body or belly and have at least two attachments to bones which may be made (1) by direct union of muscle with bone (2) indirectly by a tendon which is continuous with the muscle, or (3) by sheets of connective tissue The area at which a muscle

in view of results obtained with extremely delicate apparatus it appears that the time required for the muscle to initiate contraction after the stimulus has reached it, may be nearer to 0.004 sec, and that the time for changes associated with the development of tension or response, in the protoplasm of the muscle is even less



muscle, the more work (that is, contraction) it can perform, and the more glycogen present, the longer the muscle may be kept at work without renewal of its energy supply from external sources

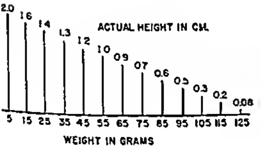


FIGURE 47

The effect of load upon contraction of the gastrocnemius muscle of the frog The work done may be expressed in gram centimeters and is obtained by multiplying the height of contraction by the weight

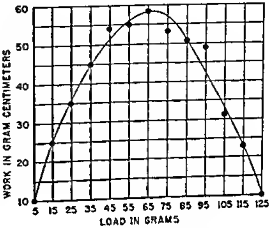


FIGURE 48

Graph of work performed by the frog's gastrocnemius muscle under different loads (from the results given in Figure 47) The optimum load is 65 grams 59 gram centimeters of work was done with this load

The work done may be calculated by ascertaining the distance (in centimeters) through which the muscle lifts a certain load (in grams) and finding the product (in gram centimeters) of the two The work done (or capable of being done) varies considerably in muscles as does the efficiency and optimum load As shown in the accompanying graph the greatest efficiency is not obtained with a minimum nor with a maximum load but with one somewhere between the two (*optimum load*) From the point of view of percentage, muscle does not seem to be very efficient the absolute efficiency occurring between 20 and 30 per cent The main reason for this low efficiency, along with many others is the great loss of energy by way of heat during the recovery period This heat cannot be converted into mechanical energy, thus, its usefulness to the muscle is lost for the most part

Work done by certain muscles such as those of a finger, can be measured —but only within narrow limits—by means of a special apparatus called an ergograph

is attached to a bone is designated as its *origin* if it is fixed, and *insertion* if the attachment is movable

Striated muscles perform work only when they contract They are so arranged that each muscle group, involved in a given movement, is closely associated with an antagonistic group An example is shown in Figure 46

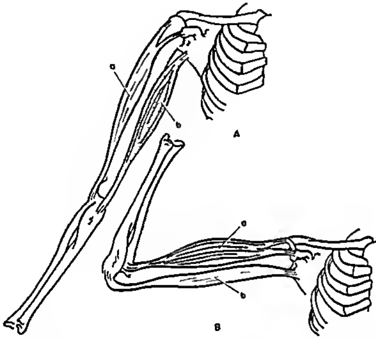


FIGURE 46

Extension (A) and *flexion* (B) of the forearm by antagonistic muscles the biceps (a) and the triceps (b) Shading indicates contraction

The *biceps* muscle of the arm has two points of origin (as its name indicates) on the scapula, and is inserted on the radius of the forearm When this muscle contracts, the forearm is flexed The antagonistic muscle, the *triceps*, has origins on the scapula and posterior surface of the humerus and is inserted on the ulna of the forearm When the triceps contracts, the forearm is extended Since these two muscles are opposite in function, it is essential that one of them must be relaxed while the other is contracted during the performance of their respective functions

Work Done by Muscles

The amount of work done by a muscle will vary with its size and the condition of its environment external and internal Thus, the larger the

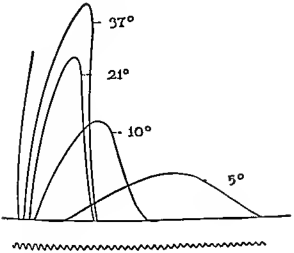


FIGURE 49

Effect of different temperatures on the latent contraction and relaxation phases of the frog gastrocnemius muscle (From Greisheimer *Physiology and Anatomy*, by permission of J B Lippincott Company)

Rigor Mortis

Soon after the death of an individual, the muscles of the body take on a state of death rigor or *rigor mortis* characterized by a loss in irritability and a rigidity of the substance of the muscle The time required for this condition to make its appearance varies considerably but is usually from 1 to 5 hrs after death There are cases where rigor sets in almost instantaneously (*cataleptic rigor*) and reports have been made that soldiers are sometimes found in rigor with their guns in position for shooting Evidently many factors may play a part in the time of onset Such circumstances as fatigue, warmth, disease, deficiency in oxygen supply and the like hasten the appearance of the condition A muscle in rigor mortis has a less solid consistency than one in rigor caloris

THE ALL OR NONE LAW

The contraction of a single striated muscle fiber, the impulse that passes over a single neuron and the contraction of the whole heart are said to follow the *all-or none law*

It has already been noted that if striated muscle is stimulated electrically with intensities between minimal and maximal, a graded response is obtained as indicated in Figure 44 (page 63) A muscle when stimulated by a current of weak intensity responds feebly conversely one stimulated by a current of strong intensity responds powerfully Since 1871 when Bowditch made the discovery it has been known that a stimulus strong enough to produce a response when applied to heart muscle produces one that is maximal There is no gradation of responses with increased stimuli the contraction is the same for a weak stimulus as for the strongest that can be

The Relaxation Period

The *relaxation period* is a reversal of the process of contraction—not a mere pulling out of the muscle due to gravity or some other physical cause It, therefore, involves activity contingent on definite chemical or physico chemical changes within the muscle cell, and these changes may be just the reverse of those involved in contraction The time required for relaxation during a muscle twitch depends on a number of factors, in a fully rested gastrocnemius muscle of the frog it is about 0 04 + sec

This results in a total of 0 1 sec for the latent, contraction, and relaxation periods of the frog gastrocnemius (compare this with 0 07 sec for rabbit striated muscle, 1 0 sec for terrapin striated muscle and 10 00 sec for mammalian involuntary muscle) Complete contraction varies considerably in muscles of different animals and in different muscles of the same organism As mentioned previously, the response of smooth muscle to stimulation is extremely slow compared with that of striated muscle

Very little research has been done on muscle physiology in the invertebrates, but, in general, big differences occur in contractions of muscles in one group of invertebrates to those of another group In one of the echinoderms, the sea cucumber, the contraction of a muscle lasts 3 sec, whereas the muscles involved in the movement of the wing of a wasp require only 5 millisec or 0 005 sec, for contraction

EFFECT OF TEMPERATURE UPON MUSCLE CONTRACTION

Both the extent and duration of contraction are affected by temperature Its effect is not the same in every case, however, if a frog gastrocnemius muscle is stimulated to contract within a temperature limit of 0 to 37 degrees C, it is found that the height of contraction increases as the temperature increases from 0 degrees C (where very little, if any, contraction occurs, since muscle loses its irritability at this temperature) to a maximum at 5 to 9 degrees C Above this temperature the contractions decrease somewhat between 15 and 18 degrees C With further increase in temperature, the contractions again increase in extent to another maximum between 26 and 30 degrees C, they then decrease rapidly up to 37 degrees C, at which temperature irritability is almost lost Above 40 to 41 degrees C in the frog muscle, and 47 degrees C in muscles of warm blooded animals, heat rigor sets in The muscle is dead that is heat rigor or *rigor caloris* is a permanent change caused by coagulation of protein material in the muscle

cle, that is, upon stimulation, the muscle fiber contracts maximally or not at all In their investigations, these men observed and photographed the movement of a droplet of mercury placed on a contracting fiber They noted that, as the stimulus is gradually increased in intensity, the fiber continues to contract to the same extent up to the point where the intensity is sufficiently great to cross over to a second fiber, causing it to contract along with the first This results in several contractions at a new level until finally the intensity is sufficiently great to affect a third fiber When the intensity is decreased the contractions decrease through the same series of steps More recent work has shown that when the limiting factor of conduction through the fiber is eliminated by using fiber length electrodes for stimulation a graded response (contraction) may be obtained with graded intensities Because of these findings, the suggestion has been made that the muscle fiber does not always follow the all or none law unless the impulse arrives through proper channels, that is, by way of the nerve and the junction between the nerve and muscle (*myoneural junction* or *muscle end plate*) It is true that ordinarily and normally the end plate is the structure which enables the muscle fiber to accept the impulses coming to it However there have been instances where the muscle end plate has completely degenerated and disappeared yet the fibers of the muscle continue to show a propagated response as described above (that is they follow the all or none law)

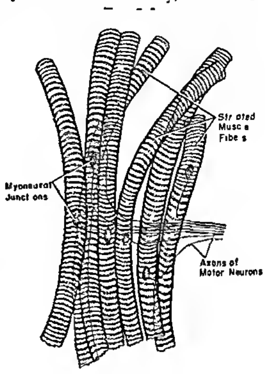


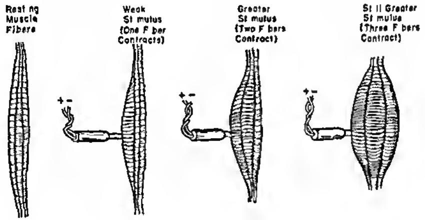
FIGURE 51

Myoneural junctions or muscle end plates

The contractile process as it is understood today, evidently does not always follow the all-or none principle but the fact that it appears to do so under normal circumstances suggests the myoneural junction as the controlling mechanism The intensity of the impulse that crosses over this junction is apparently always the same and hence, governs the extent of contraction

applied safely This phenomenon is the basis for the all or none law, the heart gives a maximal contraction to a stimulus or else it does not contract at all Some physiologists consider that the vertebrate heart functions as a single but complex cell *in the same way that a single striated fiber operates* as a single cell, although the latter has many nuclei

It has long been known that striated muscle is made up of large numbers of fibers or cells, some investigators have succeeded in separating from the whole muscle, minute parts, consisting of only a few fibers When these few fibers are stimulated, they do not show a smoothly graded increase in contraction corresponding to the gradual increase in the stimulus, but exhibit abrupt jumps from one level to another Figure 50 illustrates well the principle of the all or none law Pratt and Eisenberger, who reported this work in 1919 devised a technique by means of which a response in a



as *contracture*. The muscle tends to stay in what appears to be a contracted condition. However, it soon fatigues, and finally fails to contract at all. The awkwardness and poor control of a fatigued human muscle are owing partly to fatigue contracture. Coldness also results in contracture very similar to that caused by fatigue. This is quite noticeable when an attempt is made to write in a warm room after the hands have been subjected to extreme cold; it is not so difficult to contract the muscles used in writing but relaxation proceeds at a very slow rate. If a frog is injected with a solution of the drug veratrine, its movements soon become clumsy. Close examination of the animal shows that the muscles may be contracted normally, but relaxation proceeds very slowly. This contracture can be observed if a muscle is isolated and studied in the usual way; evidently, it is not the result of continuation of impulses coming from the nerve.

FATIGUE

In fatigue, it appears as though muscles use up their immediate supply of fuel (glycogen) or that the waste products which have collected during contraction in some way cause the muscles to 'fatigue.' In fact, both of these factors add to the process but this evidently is not the whole story. It has been shown, for example, that when a muscle is caused to contract until fatigued, by stimulation with direct current, it will continue to contract if the current is reversed. Perhaps changes in the physico-chemical state of the muscle are more directly responsible. This seems to indicate that the accumulation of waste products is not the only factor in the onset of fatigue.

SUMMATION AND TETANUS

The phenomenon known as summation plays an important role in muscular movement. If two subminimal stimuli are applied to a muscle, one immediately following the other, the muscle, which fails to contract on application of the first subminimal stimulus, contracts when a second subminimal stimulus is applied (or possibly several subminimal stimuli may be necessary before the response occurs). It is clear that an effect is induced by two or more stimuli which cannot be brought about by one stimulus alone. The action of the second seems to be added to or superimposed on that of the first. This effect is known as *summation of stimuli*, a phenomenon characteristic of all excitable tissue.

Human muscular contractions as used in movement and locomotion, are not, as the discussion so far might imply, mere single contractions of muscles, which last only a short time, but are a summation of a number of

Since muscle fibers normally follow the all or none principle, it is postulated that when a muscle contracts greatly, a much larger number of fibers are contracting than when the muscle gives a weak contraction In other words, the extent of whole muscle contraction depends upon the number of fibers contracting The fibers that do contract, however, are doing so to their greatest extent

TREPPE OR STAIRCASE PHENOMENON AND CONTRACTURE

It has been found that the maximal contraction of the muscle fiber is not always of the same magnitude In fact there is usually a graded response to the first several stimuli applied to a rested muscle to which the term *treppe* is given If a freshly excised muscle is made to contract by a succession of stimuli, all of the same intensity, there is a gradual increase in the extent of the contraction up to a maximum Because of the appearance this phenomenon produces when recorded on a slowly moving kymograph drum, the name 'Treppe (from the German word for staircase) has been applied to it It may be the result of increase in heat or of increase in the hydrogen ion concentration or of other chemical changes brought about by the first contractions It should be noted that tension (stretch) also is associated with the magnitude of contraction

Figure 52 shows a record, made on a slowly moving kymograph drum,

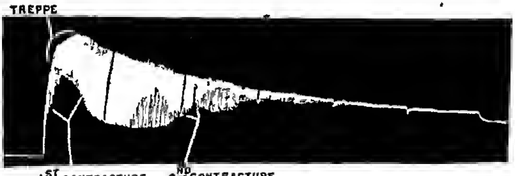


FIGURE 52

Treppe and contracture The stimuli were given at the rate of about 1 per second and the muscle contractions recorded on a slowly moving drum

of a muscle responding to maximal stimuli applied at the rate of two per second Since the muscle was a fresh one, the Treppe phenomenon makes its appearance during the first few contractions If stimulation of the muscle is continued, it contracts fully for some time but soon the tendency to relax in the contracting muscle gradually diminishes This is known

The fact that the muscle during complete tetanus responds to each impulse that comes to it can be demonstrated by observing the passage of the impulse (*action current*) along with the tetanized muscle. There is an action current (page 84) for each stimulus even in the absence of a visible contraction.

If approximately 16 stimuli per second are applied to a frog gastrocnemius muscle, the contractions are fused as illustrated in the figure. With less than 16 stimuli per second a gradation of responses is obtained and

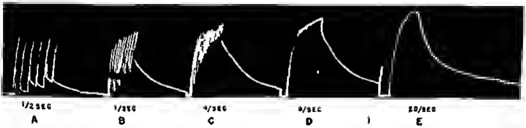


FIGURE 54

Development of tetanus. A, muscle contracts and relaxes completely. B, C, and D, incomplete tetanus. E, complete tetanus. The number of stimuli applied per unit time are indicated.

if a stimulus is given every one or two seconds, there is no fusion of contractions.

The number of stimuli needed in unit time to produce tetanus vary considerably depending on the animal and the muscle. Tetanus is difficult to produce in insect wing muscles; it may take several hundred stimuli per second. In the cat, it takes about 30 per second for the soleus muscle and 100 per second for the gastrocnemius.

It has long been known that in human muscle the contractions are mainly tetanic in character. Early evidence for this assumption was presented in 1810 by Wallaston, who actually listened to the tone produced by contractions of his muscles. He accomplished this by introducing one finger into the ear and then forcibly contracting the muscles of the arm; he could hear a dull murmur and concluded that the sound corresponds to a frequency that oscillates between 14 to 15 per second at the minimum and 35 to 36 maximum.

Helmholtz (1864) also investigated the subject of muscle sound. He noted that during the "dead of night" if the masseters or chewing muscles are forcibly contracted at the same time the auditory meatuses are closed, a murmur is heard that lasts as long as the contraction. He stated that the tone corresponds to 36 to 40 vibrations when the masseters are forcibly

contractions In fact all the voluntary muscle contractions that occur in the body are prolonged contractions as compared with a single muscle twitch In other words along with summation of stimuli in muscle studies, there is a phenomenon known as *summation of contraction* If an isolated muscle is stimulated so that it contracts and if immediately after the refractory period, it is again stimulated, a further contraction takes

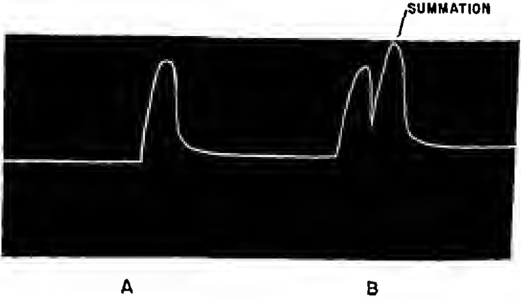


FIGURE 53

Summation of contraction in the frog s gastrocnemius muscle A single stimulation B double stimulation the second stimulus given about 0 06 sec *after the first* Note that the second contraction is greater in extent than the first

place which may be partially or completely superimposed upon the other The stimuli may be given in such rapid succession that the responses are fused to produce a sustained contraction This type of sustained response is referred to as *tetanus* and the stimulus that produces it as *tetanic stimulation*

Volta (1792) discovered the fact that frequently repeated stimuli were able to produce sustained contraction in muscle and Matteucci (1838) first called this state of contraction tetanus The different contractions cannot be distinguished unless tetanus is incomplete in which case the tendency of the muscle to relax between each stimulus is quite noticeable *Incomplete tetanus* may occur if too few stimuli are received by the muscle That is, summation may occur but there is no complete fusion between contractions

the first to the second point on the muscle In this case the distance between the two levers was 15 mm, so that the wave traveled 15 mm per 0 03 sec (about ½ meter per second)

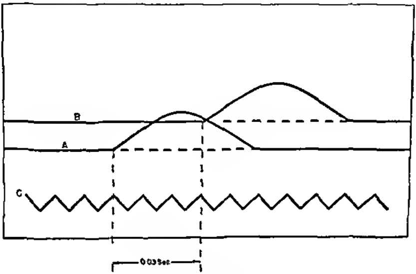


FIGURE 56

Determination of the speed of the contraction wave Two records obtained from the same muscle with a single stimulus (arrangement as illustrated in Figure 55 with levers 15 mm apart) A movement of lever nearest point of stimulus B movement of lever 15 mm from first C tuning fork record 100 vibrations per second

The progress of the wave may vary greatly, depending on the strength of stimulus state of excitability, extent of fatigue, and temperature

TONUS

In the living organism whole skeletal muscles are seldom completely relaxed but exhibit tonus which has been defined as *the continued action of muscle*, it is a partially sustained contraction

If a decapitated frog is suspended from a muscle clamp and if the nerve leading to the leg is cut on one side, the two hind limbs assume different positions The leg of the side on which the plexus was cut hangs limply and fully extended but the leg on the opposite side, where the nerves are intact is slightly contracted because of *tonus* The word tone signifies a persistent rather moderate degree of activity

In mammals, as well as in many other groups, the muscles concerned with posture are good examples of skeletal muscles which exhibit tonus The striated muscles of wild animals must be held in a ready condition by their partial contraction or tonus Actually, one of the best examples

closed The vibration presumably corresponds to the number of impulses that reach the muscle per second

VOLUME OF MUSCLE DURING CONTRACTION

In early muscle investigations, it was believed by some that the muscle during contraction actually increased in volume However, this is a fallacy, muscles do not increase in volume at all during contraction As a matter of fact, it has been shown more recently that there is a very slight decrease in muscle volume, the muscle losing approximately 1/20,000 of its weight

CONTRACTION WAVE

If a muscle is stimulated artificially the contraction spreads over the muscle from the point of stimulation The rate of propagation or passage of the contraction wave can be measured by placing the arms of heart levers (Figure 55) at two different points on a muscle and then stimulating at

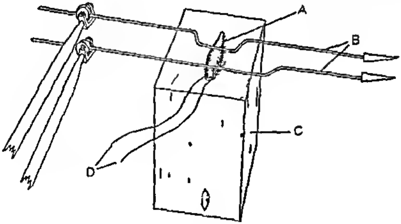


FIGURE 55

Arrangement of the heart levers on a gastrocnemius muscle in studies on the propagation of the contraction wave over the muscle A gastrocnemius muscle B heart levers bent in such a way that one celluloid writing point is just beneath the other C block of wood for holding muscle D wires leading from an inductorium and connected to the pins which pass through the muscle into the wood and then act as electrodes for stimulating the muscle (From Pace and Riedsel *Laboratory Manual for Vertebrate Physiology*)

one end The accompanying Figure 56 gives such a record by means of which the rate can be calculated

The second curve rises about 0 03 sec after the commencement of the first curve Therefore the wave of contraction took 0 03 sec to pass from

as a dog, yet the pressure in the stomach returns almost immediately to its original level because of the change in tonus in the muscles of the stomach wall The same adaptation occurs when food is introduced into the stom ach, the length of the muscle changes as the cavity fills, and the pressure therefore remains the same Ultimately, the pressure does increase and may be associated with peristaltic waves which aid in forcing out the con tents The uterus during pregnancy is another excellent example of tonic contraction As the embryo and fetus develop, the size of the uterus in creases without pressure change until parturition (child birth) The in crease in size is owing to loss of tonus and increase in size of muscle cells

MECHANISM OF TONUS

The actual mechanism of true tonus is not understood An early sug gestion was that some sort of a 'catch mechanism" might be present so that once the contraction is made it stays in the contracted state with very little expenditure of energy

Bayliss (1920) suggested the principle of the catch mechanism which is represented by the structure shown in Figure 57 The teeth glide over

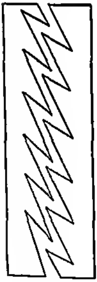


FIGURE 57

Diagrammatic representation of the so-called 'catch mechanism theory of tonus according to Bayliss Energy is required to move the two structures but once they reach a certain position they may be held there without any further expenditure of energy Energy is required to separate the two blocks and return them to their normal position Muscle supposedly develops tonus and maintains it with out much loss in energy because of a unique configuration within the molecules that tends to hold it in a partially sustained contraction

one another if pulled in one direction but in the opposite direction they will catch and hold until energy is applied to release them An attempt has been made to apply such an explanation to the mechanism of muscle tonus

The 'colloid theory ' of tonus has been advanced also and might account

of tonus that can be found is in the partially contracted state of smooth muscles

Tonus differs from tetanus in several ways, (1) the contraction is usually only partially sustained, (2) oxygen consumption is very low, (3) contraction is maintained indefinitely without apparent fatigue, (4) action currents are not so noticeable in tonus

TONUS IN INVERTEBRATES

Tonus is well exemplified in the muscles of invertebrates such as the mollusks The muscles of some bivalves (clams, *Pecten*, and the like) consist of two types, striated and smooth The striated muscles act at about the same speed as the frog gastrocnemius muscle, and are used for sudden, rapid closure of the shell and (in *Pecten*) for flapping the valves thus producing movement through the water On the other hand, smooth muscle fibers are very slow in their action and sometimes maintain tension for long periods of time They may take from 30 sec to 60 min to relax Certain features of tonus in smooth muscles of mollusks and in vertebrate smooth muscle are somewhat similar but the tensions reached in those of the former are very much greater

A clam can be held out of water for several days with a heavy weight attached to the shell, yet still remain closed It has been calculated that if these contractions were similar to tetanic contractions the clam would need so much material for fuel that it would take at least an amount of glycogen nine times greater than the dry weight of the clam itself to maintain the tonic contraction During the actual shortening process when the clam is closing its shell, relatively large quantities of energy are needed (this evidently involves the contraction of the striated fibers) but once the shortened state is reached, it is maintained without effort and with a minimum expenditure of energy

TONUS IN SMOOTH MUSCLE OF MAMMALS

In the case of mammals, excellent examples of tonus are furnished by the smooth muscles of the stomach, intestines, urinary bladder, walls of the arteries, and other organs Tonic adaptation is a characteristic and important property of smooth muscle

Because smooth muscle can alter its tonic condition readily, it may exist one moment at one length, and the next at another, yet with equal degree of tension For this reason, the pressure in the urinary bladder may be the same whether its contents consist of 50 or 150 cc of urine Likewise 400 to 600 cc of water can be forced into the stomach of an animal such

as a dog, yet the pressure in the stomach returns almost immediately to its original level because of the change in tonus in the muscles of the stomach wall The same adaptation occurs when food is introduced into the stomach, the length of the muscle changes as the cavity fills, and the pressure therefore remains the same Ultimately, the pressure does increase and may be associated with peristaltic waves which aid in forcing out the contents The uterus during pregnancy is another excellent example of tonic contraction As the embryo and fetus develop the size of the uterus increases without pressure change until parturition (child birth) The increase in size is owing to loss of tonus and increase in size of muscle cells

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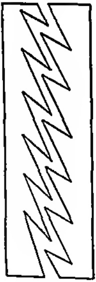

FIGURE 57

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one another if pulled in one direction but in the opposite direction they will catch and hold until energy is applied to release them An attempt has been made to apply such an explanation to the mechanism of muscle tonus

The ' colloid theory of tonus has been advanced also and might account

for something related to a so called "catch mechanism" in muscle, that is, the contracted and relaxed states differ entirely in colloidal structure During contraction the colloidal state of the muscle changes, which requires considerable energy, and the new structure is held for some time, with a minimum energy requirement

Another theory implies that in tonus of vertebrate smooth muscle only a small number of fibers are active at any one time and, when fatigue lowers their excitability, they relax, causing adjacent fibers to stretch The most excitable of these may contract (the most excitable would be those which have rested for the longest period) The muscle is supposedly held in tonus by constant repetition of this procedure This would be a degree of tetanus, however, and if this were the case, it is certain that more energy would be utilized than can be accounted for in the occurrence of tonus A satisfactory solution of the tonus problem is yet to be found

MICROSCOPIC STRUCTURE OF MUSCLE FIBER AND FIBRIL

The gross structure of the striated muscle fiber has already been described briefly, but in order to understand the action of muscle and the processes involved in that action, it is desirable to have a greater knowledge of the microscopic structure of the fiber The cross striations or bands of the muscle cell are readily seen under high power, the light bands alternating with the dark The light bands are sometimes referred to as *isotropic* and the dark, *anisotropic* (or birefringent) bands These terms have been applied because the light bands, when viewed during exposure to polarized light (light which passes through crossed Nicol prisms), appear dark and the dark bands appear light, they are singly and doubly refracting, respectively It was once thought that the whole muscle cell was anisotropic, but subsequent close examination with improved microscopic technique revealed otherwise The dark or anisotropic substance appears to fill the muscle fiber during the contracted state which may have given rise to the false impression that the whole muscle was doubly refracting If muscle fibers are fixed (killed quickly) in absolute alcohol or osmic acid solutions, they may be caught in various degrees of contraction

Upon observing these fibers under the microscope, Engelmann (1878) came to the conclusion that the anisotropic substance swells during contraction, whereas the isotropic substance decreases in volume He maintained that the anisotropic substance subtracts water from the isotropic Other scientists later came to the same conclusion In Figure 59, it may be noted (in fibrils of insect muscles) that the substance of the dim band swells and migrates

Upon closer observation of the fiber, the muscle fibrils (*myofibrils*) can be seen, especially if the fiber is torn a bit and teased with a dissecting needle The cross striations are also found in the fibrils A protein, *myosin*, is the chief but not the only constituent of the fibril It may function in the formation of protein fibers, the arrangement of which may be responsible for the actual shortening A diagram of a muscle fibril is shown in Figure 58

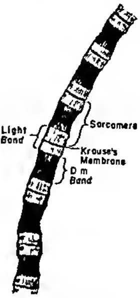


FIGURE 58

Diagram of an electron micrograph of a simple myofibril

Structure of Sarcomeres

The fibril is divided into disclike structures called sarcomeres, in the center of which is located a dim band The division is made by a double membrane, Krause's membrane (Z disc), which is continuous across the whole fiber and appears to bisect the light or clear substance In other words, the fibril may be looked upon as a succession of segments or sarcomeres (the actual units of muscle structure), and the contraction of the fibril as the sum of the contractions of the sarcomeres The contraction of the fiber, in turn, is therefore the sum of the contractions of the fibrils, and the contraction of the muscle, the sum of the contraction of all the active fibers

Because of the arrangement of the sarcomere, it has been suggested that the term "stratified" be applied to this type of muscle instead of "striated"

The sarcomere contains many different types of substances, both colloid and crystalloid The crystalloids are chiefly potassium chloride and potassium phosphate which are found for the most part in the dim band, or Q disc, as it is sometimes called Naturally there are many proteins and carbohydrates, and on close observation granules can be seen which are probably lipoid in nature They may function as reserve foodstuffs

Changes in Fibrils and Sarcomeres during Contraction

It was noted previously that if muscles are suddenly fixed in solutions of alcohol or osmic acid, the fibers may be caught in various degrees of contraction As indicated in the figure of an insect striated muscle, the dim or anisotropic substance appears to fill the sarcomere in the completely contracted fiber This is not the case, since by stretching the fiber it can

be seen that the light substance still remains, although its volume has decreased considerably

During contraction in *muscle fibrils* (or *sarcomeres* of fibrils) the following changes take place The dim or anisotropic substance divides, one half migrating to one end of the sarcomere and the other half to the opposite end In the meantime, the sarcomere is *shortening* and broadening (Figure 60) The dark substance increases in volume but it is not known for

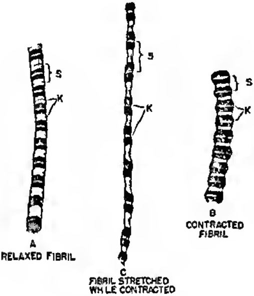


FIGURE 59

Diagram of muscle fibril of an insect illustrating the increase in volume and movement of the dim substance when a fibril contracts (after Schafer) S sarcomere, K, Krause s membrane

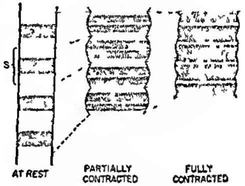


FIGURE 60

Diagrams of muscle fibril illustrating the change in the sarcomere during contraction The b section and migration as well as increase in the volume of the dim substance are indicated S sarcomere

certain whether or not it does so at the expense of the sarcoplasm surrounding the fibril or at the expense of the light substance in the sarcomere, possibly the latter

THE ACTION CURRENT OF MUSCLE AND NERVE

The excitatory and conductile processes (reception and action currents) in muscle and nerve are very similar and for this reason they will be considered in relation to both structures *If*, *when a nerve or muscle is stimulated*, electrodes from a galvanometer (an instrument for measuring minute electrical charges) are placed at a position beyond the point of

stimulation, a current can be detected running along the tissue This is called *the action current* and is produced by a difference of potential at the surface of the nerve or muscle The discovery of the existence of such a current is credited to Galvani (1786), who noticed that an electric current was produced when two different metals were brought in contact with the nerve or muscle of a frog

The story is sometimes told that Galvani was buying some special dainty for his sick wife at a butcher shop He noticed that the frog legs, hanging on copper hooks attached to an iron bar contracted every time a gust of wind entered the shop and caused them to swing against the iron bar In other words every time the muscles came into contact with the bar, they contracted He concluded that the muscles of the frog were charged as is a Leyden jar, with an external negative and an internal positive charge He assumed that since there was contact between the two metals (copper and iron) every time the muscle closed the circuit by swinging against the iron bar, a current was produced which caused the contraction It was suggested however that Galvani s interpretation was incorrect since a circuit would be produced by the two different metals in any case In other words although the current produced was not owing to any action current or action potential of the muscle or nerve Galvani believed that this was the case Thus his interpretation of the results was erroneous but the conclusions which he drew from these results and interpretations were correct Bernstein (1871) was the first to show that there is a very close relationship between the electrical and the mechanical response but it was not until 1926 that Fulton proved definitely that the electrical response of all excitable tissues just precedes the mechanical response

THE ACTION CURRENT AND THE IMPULSE

The electrical response mentioned above is the same as the impulse or action current Figure 61 a record taken from Fulton s report on the electrical and mechanical response of the gastrocnemius muscle of the frog shows the relationship between the action current and the impulse A single induction shock was applied to the muscle and then a short time later this was followed by a rapid succession of six shocks (or stimuli) These stimuli are recorded in such a way as to show their relation to the mechanical response A contraction obtained with a single stimulus is much weaker than the short tetanic contraction obtained with six shocks In the latter case the stimuli are quite separate and distinct but the contractions are fused It is apparent that the electrical response precedes the contraction of the muscle the former is just about completed before the latter

begins This, of course, is fairly good evidence that the current and the impulse are one and the same and are now regarded as such

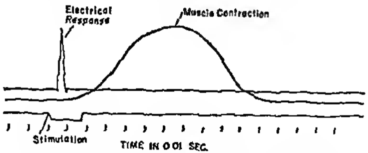


FIGURE 61

Illustrating the relation between the mechanical response (contraction) and the electrical response of a frog s gastrocnemius muscle The electrical response (impulse) follows stimulation and just precedes the contraction (after Fulton)

ANIMAL ELECTRICITY

Some animals have taken advantage of the ability of their tissues (especially muscle and nerve) to produce an electrical current and use it for other purposes aside from its use in muscle contraction or nerve conduction Special electric organs are found in certain species of fish which can produce electric currents with electromotive forces that may become as high as several hundred volts They use these structures for warding off enemies or for stunning prey The electric organs are made up of modified, striated muscle cells which can evidently store up electrical energy, in the same manner as does a storage battery, and release it when necessary The nerve trunks that lead to these modified muscles are enormous and may be an indication of the method by which charges are built up within these organisms

THE DIPHASIC RESPONSE

If the electrodes (nonpolarizable) of a galvanometer are placed upon an uninjured nerve or muscle, the action current will be recorded by the instrument as a *diphasic response* (actually a movement of the galvanometer needle first to one direction, then in another) The movements of the galvanometer indicator are such that on reproducing them graphically a diphasic wave would result This is illustrated in Figure 62 which indicates the direction of movement of the action current along the nerve or muscle. When it passes under the first electrode (left) it results in a

negative response in relation to the other electrode, there appears to be a short period of inactivity when no current can be detected This is owing to the arrangement of the electrodes, it takes a fraction of a second for the action current to pass over to the second electrode which is affected

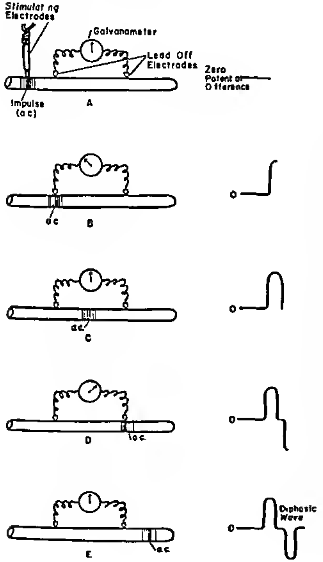


FIGURE 62

Illustrating the detection of the action current of muscle or nerve by means of a galvanometer which registers it as a *diphasic wave* that is the movement of the galvanometer needle to the left when the action current (a c) passes under the left lead off *electrode is registered as* an upright curve while the movement of the needle to the right when the current reaches the right electrode is registered as an inverted curve A stimulus is applied to nerve or muscle B the negative (or neutral) action current has reached the first electrode C the action current has passed by the first electrode and the curve dropped back to zero D action current has reached second electrode curve or wave is indicated as being inverted E action current has passed second electrode At zero potential difference the charges on the lead off electrodes are the same therefore no difference is registered

and to cause the galvanometer indicator to move to the opposite side of the zero point

CURRENT OF INJURY AND THE MONOPHASIC RESPONSE

When tissues are injured a negative potential called the *current of injury* is always produced at the point of injury Actually, this difference may

phenomenon, known as electrotonus, is explained by the charges that accumulate at the two poles when a current passes through the living tissue, it is the altered physiological condition (a polarization) of the nerve or muscle at the poles The condition at the anode is known as *anelectrotonus* and that at the cathode, as *catelectrotonus*

If a current, too weak to stimulate, be applied to a nerve or muscle, it is found that there is an increase in positive charges at the anode (the positive pole) and in negative charges at the cathode (the negative pole)

ADDITIONAL READING

Houssay, B A, *Human Physiology* (McGraw Hill 1951), chs 67, 68 Excitation and contraction of muscle

6

The Chemistry of Muscle Contraction

MUSCLE is a tissue which can transform chemical energy into the mechanical energy necessary for contraction The heat production and the chemical processes involved in this conversion of energy are so closely linked that they necessarily must be considered at the same time

The history of the development of knowledge concerned with the energy relationships within muscle is a very interesting one, and it may be added, that much of the information necessary to describe adequately all of the functions which occur is still lacking The present discussion is concerned only with some of the more salient discoveries and their relation to each other It is essential first however, that one is made familiar with the type of chemical substances which will be considered in the study of muscle contraction

CONSTITUENTS OF MUSCLE

The chief constituents of muscle are as follows

1 *Water* the most abundant constituent of muscle, makes up about 75 per cent of its mass Certainly not all of this water is present in the same form some of it may be lost without disrupting the general nature of the protoplasm A greater portion of the water of the muscle, however, is in some way so intimately associated with other molecular constituents, that if it is lost, then death of the tissues may very well result

2 *Proteins*, of which there are several types—myosin, actin, myogen, and muscle hemoglobin (myoglobin) to mention a few—make up about 20 per cent of the muscle According to present day thinking the proteins, myosin and actin are of great importance in the contraction process, and their coexistence is a prerequisite for proper function The myosin molecule appears to be aligned with its long axis parallel to that of the fibril, and possibly in greater concentration within the anisotropic substance of the dark band Myogen is of much lesser viscosity than myosin, and occurs in the sarcoplasm The function of muscle hemo-globin is discussed later (page 100)

3 *Carbohydrates* may account for as much as 1.0 per cent of the muscle weight The most important carbohydrate is glycogen which is derived

from glucose of the blood and stored as fuel for muscle contraction It was discovered by Claude Bernard during the middle of the nineteenth century

4 *Fats* vary considerably and are found chiefly in the connective tissue of the muscle framework although some cholesterol and phospholipids may be found in the muscle fibers

5 *Nitrogenous extractives* may be present as the end products of metabolism or as substances very essential for contraction these substances are discussed in detail later (page 94)

6 *Non nitrogenous extractives* such as lactic acid and inosite, are also present, their concentrations varying considerably

7 *Enzymes* in reality are proteins but, because of the known specificity of their action they are considered separately

8 *Inorganic salts* such as those of calcium magnesium potassium and sodium which are quite essential for the activity of the muscle enzymes are present in much lesser quantities

POSSIBLE ROLE OF OXYGEN IN CONTRACTION PROCESSES

Many theories have been advanced from time to time to explain the source of energy for muscle contraction

The work of Fletcher (1902) stands out as one of the earliest contributions to progress toward our present understanding of the proper energy relationships He discovered that a muscle could do work in the total absence of oxygen at the expense of energy stored within the tissue Records obtained by repeating Fletcher s experiments are presented in Figure 64 He showed that no foodstuffs were oxidized in the direct production of energy for contraction that is when he placed an excised frog muscle in nitrogen and repeatedly stimulated it the muscle contracted and continued to do so for some time before signs of fatigue appeared However the muscle can contract for a longer period in the presence of oxygen and will recover quite significantly if it is rested for at least 5 min before being stimulated again This is not true for the muscle that is exposed to pure nitrogen even after long periods of rest a second series of contractions could not be affected after the initial fatigue

It was thus shown that oxygen is not essential for the contraction of muscle but rather for its recovery Lactic acid which forms during contraction disappears only in the presence of oxygen It was known long before Fletcher s discovery that an isolated muscle which has been contracting for some time has a decidedly acid reaction It was known also that lactic acid is produced in a muscle during rigor mortis It was not until

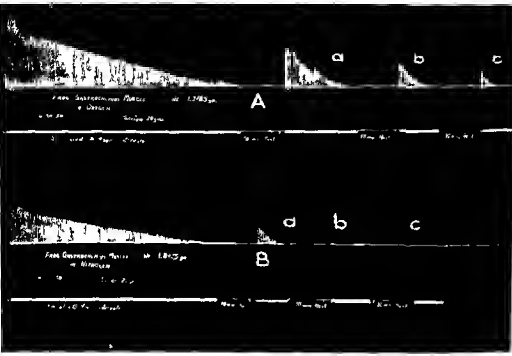


FIGURE 64

A repetition of Fletcher's experiment. A, contractions of frog gastrocnemius muscle when exposed to oxygen. After fatigue it was allowed to rest and was then stimulated again at a, b, and c after a 10 minute rest period; partial recovery is evident. B, contraction of frog muscle placed in pure nitrogen. There is only partial recovery following first 10 minute rest period and no recovery thereafter.

1907, however, that Fletcher and Hopkins first observed the production of lactic acid during the normal contraction of muscle. For years this chemical process, resulting in the formation of lactic acid, was the only one that could be demonstrated during contraction of muscle. These two men were also the first to suggest that, since lactic acid disappears in the presence of oxygen, it must be resynthesized into its precursor, glycogen; their evidence for this theory was not sufficient, however.

OXYGEN DEBT AND LACTIC ACID FORMATION

The fact that the body has the ability to incur "oxygen debt" makes possible large productions of energy such as are needed for exercise.

In the earlier work on muscle, one of the first changes to be noted during contraction was utilization of oxygen. Oxidation is the most pronounced of all the chemical processes in muscle. An adequate supply of oxygen is essential if the muscle is to continue its contractions over a long period of time. It has already been pointed out that muscle can be caused to

contract for short periods in the absence of oxygen; that in its presence fatigue does not appear so rapidly. Thus, oxygen is required for a recovery process which is continually recurring within the muscle, but which cannot proceed at a rate sufficient to keep up with the needs of the tissue during extended activity. During exercise, for example, the body does not take in sufficient oxygen to oxidize completely the glycogen necessary for the extra energy needed. As a result, the glycogen breaks down anaerobically—releasing the energy required, but forming intermediary products, one of which is lactic acid which accumulates in the muscles until such time as sufficient oxygen is taken into the body to oxidize the acid completely. This accumulation constitutes the oxygen debt which is paid off when the muscles cease contracting in exercise or work. A condition of partial or complete fatigue is said to exist, depending on the amount of lactic acid that has collected in the muscle. That this is at least partly true can be shown by suspending a frog muscle in Ringer's solution and stimulating it to contract anaerobically several times per minute; there is very little accumulation of lactic acid, for there is sufficient time for it to diffuse into the solution. Under these conditions the muscle does not show fatigue until its glycogen has disappeared. During normal life activities, the rate of work is usually slow enough so that the lactic acid is burned as rapidly as it forms, but during exercise the rate of formation is sufficiently rapid to cause this substance to collect. Thus a man who has been running for several minutes will incur a considerable oxygen debt. The lactic acid which has been produced continues to be oxidized for a long time after the man has stopped running. If the muscles of the human body performed work in the same way that it is performed by a combustion engine, that is, only in proportion to the amount of oxygen supplied, even the mildest exercise could not be tolerated unless man possessed a heart and lungs sufficiently large to supply him with the needed oxygen. Since the muscles can go into oxygen debt, however, great contraction is thereby possible.

HEAT PRODUCTION IN MUSCLE

Much of the earlier knowledge concerning the energy relationships in muscle during activity may be attributed to the work of A. V. Hill and the continuation of his studies and formulation of theories by Otto Meyerhof. Hill worked chiefly on heat production in muscle. He perfected the *thermopile* so that it could be used with much greater precision in the detection of heat changes in muscle during or after contraction. The early type shown in Figure 65 was used for the gastrocnemius muscle of the frog.

The temperature of a muscle is not raised more than a thousandth of a degree centigrade, with so slight a change an electrical method of measurement is necessary The thermopiles which are used for this purpose are made of two wires of different metals Hill in his earlier type used iron

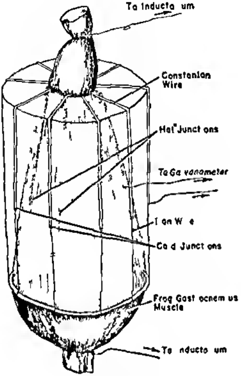


FIGURE 65

Type of thermopile used in the early work of A V Hill *The muscle comes into* contact with the hot junctions of constantan and iron wire The cold junctions are on the outside The same principle is still used in the more modern thermopiles

and constantan wire but in the more modern types copper and constantan are employed The wires are joined at two places so as to have two junctions the one to be used as the cold junction and the other as the hot junction The cold junction is held at a constant temperature below that which exists in the muscle while the hot junction touches the muscle An increase in temperature at the hot junction results in a greater change in the potential difference between the two metals This is recorded on the galvanometer

By means of this apparatus it has been found that there are two chief phases of heat production during muscle activity (1) *initial heat* and (2) *delayed heat* These two phases have been analyzed further so that the initial heat may be divided into (a) *contraction heat* which occurs during tension and (b) the *relaxation heat*, which begins during the relaxation period Both of these can occur in the absence of oxygen

After the contraction is over, the delayed heat makes its appearance

This also appears in two phases (a) the *delayed anaerobic heat* which, along with the contraction and relaxation heats, appears in the absence of oxygen, (b) the *oxygen recovery heat* is by far the greatest of all These phases, with their relative values, are best expressed as follows

Phase	*Relative Value* (initial heat = 100)
1 Initial heat	100
a Contraction heat	65
b Relaxation heat	35
2 Delayed heat	124
a Delayed anaerobic heat	8
b Oxygen recovery heat	116

Since all of these heat phases coincide with chemical changes in the muscle, a proper appreciation of the former prepares the way for a more thorough comprehension of the occurrence and time of occurrence, of the chemical processes during muscle contraction

FORMATION AND DECOMPOSITION OF LACTIC ACID DURING CONTRACTION

The fact that lactic acid forms during muscle contraction as the result of breakdown of glycogen was proven by Meyerhof (1919) He observed that the glycogen content decreases as the lactic acid increases and that only a small amount of the lactic acid is burned In his tests he found that approximately four fifths of the lactic acid is resynthesized to glucose (or glycogen) at the expense of energy produced by the oxidation of the remaining portion (approximately one fifth of the lactic acid) Thus the association of lactic acid accumulation and oxygen debt to muscle fatigue may be explained on the basis that glycogen stores are not re established so that activity could be continued

Glycogen is sometimes referred to as animal starch and is supposedly made up of 12 to 15 molecules of simple sugar in contrast to plant starch which is made up of 24 or more of these molecules Carbohydrate is stored in the body as glycogen Certain enzymes are capable of releasing the glucose in a soluble form for body use which reacts with phosphoric acid in various combinations Finally this hexosephosphate, as the com bination may be called is broken down into lactic acid It is the energy produced by this breakdown that Hill and Meyerhof erroneously asso ciated with the mechanism directly concerned with contraction

So certain were these early workers that lactic acid was formed during or instantly preceding the contraction that by 1924 it was thought that

the greater mysteries concerned with the chemistry of muscle contraction were solved. It is now known that this early conception was incorrect. Even today, investigators are far from "closing the book" on this particular chapter. However, it is interesting to note the conclusions of these men, correct as far as they have gone, which may be expressed and summarized as follows:

Anaerobic Phase

Glycogen $\xrightarrow{\text{phosphorylase}}$ Hexosephosphate $\longrightarrow$ Lactic acid + H_3PO_4 + energy

$\boxed{\text{This energy was supposed to be used directly for contraction}}$

Aerobic Phase

Lactic acid (one fifth of that produced) + $O_2 \rightarrow CO_2 + H_2O$ + energy

$\boxed{\text{Aids in the resynthesis of glycogen from lactic acid}}$

Lactic acid (four fifths of that produced) $\longrightarrow$ Glycogen

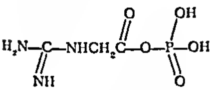
None of the above reactions are "explosive" enough to account for the rapid contraction that occurs almost instantly upon the reception of the impulse from the nerve fiber. For a long time it was thought that hexosephosphate (often referred to as lactacidogen) was a substance that could change explosively, but many investigators doubted this. This doubt was soon substantiated when it was discovered that lactic acid does not appear until after contraction begins. Therefore, the energy produced by its formation could not possibly be that used directly in the muscle for contraction. The question was again raised as to what chemical change could produce energy for the development of tension.

THE ROLE OF PHOSPHAGEN IN CONTRACTION

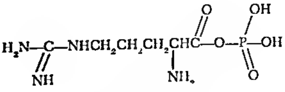
In 1927, it was discovered that a substance, called *phosphagen*, breaks down during muscle contraction to form creatine and phosphoric acid, which materials can reunite to form the original compound. Creatine is methylguanidine acetic acid which is distributed in animal tissue and is especially abundant in vertebrate striated muscle as phosphocreatine or phosphagen. Creatinine, a waste product of muscle metabolism and an anhydride of creatine, is a normal constituent of urine.

Invertebrate phosphagen consists of phosphoric acid and arginine, which is closely related, chemically, to creatine. In fact, some investigators have

suggested that, from an evolutionary point of view, creatine phosphate may have been derived from arginine phosphate, but there is no satisfactory evidence for such a derivation The formulae of the two compounds are presented below



Creatine phosphate



Arginine phosphate

The action of the two types of phosphagen are the same Generally speaking, phosphocreatine is usually associated with vertebrate and arginine phosphate with invertebrate muscle, but both are found in the muscles of the primitive *Chordata*, such as the class *Enteropneusta* (*Balanoglossus*), and of the *Echinodermata*, such as the classes *Echinoidea* (sea urchins) and *Ophiuroidea* (sea cucumbers) These primitive chordates are more nearly related to the vertebrates than to invertebrates However, the fact that phosphagen in the form of phosphocreatine and arginine phosphate is found in both chordates and echinoderms would suggest, at least physiologically in this respect, a close relationship between the two phyla and thus presents a clue to possible evolution

In 1930, Lundsgaard performing experiments on muscles poisoned with *mono iodoacetic acid* proved that the muscle was capable of contracting although lactic acid was not produced since the enzymes concerned with its formation were inactivated This substantiated the theory that lactic acid production was not associated with the energy furnishing reactions for the contraction A muscle exposed to mono iodoacetic acid will contract on stimulation and may give as many as 90 twitches before going into rigor It is interesting to note that while the contractions last they are normal in relation to the latent period the duration of the twitch the development of tension and action current However, the muscle was not capable of doing as much work as a normal muscle, and a difference was observed in the content of free creatine and phosphoric acid after the muscle was fatigued At first it would appear that the energy for the contraction process originated from phosphagen breakdown, since it could not be correctly resynthesized by energy derived from the proper utilization of lactic acid, the muscle would fatigue at a more rapid rate, and could not recover from fatigue during rest However, at that time doubt still remained as to whether phosphagen furnished the contraction energy

SUMMARY OF PRESENT KNOWLEDGE OF AEROBIC PROCESSES IN MUSCLE

The source of energy utilized directly in contraction is still uncertain, but, with the discovery of *adenosine triphosphate* in 1928, it was thought that a material might have been found which would have its energy available in such a form that it could be furnished in great amounts instantaneously. Adenosinetriphosphate (ATP) may release one molecule of phosphoric acid to form adenosinediphosphate (ADP) and this substance in turn may break down further with the release of another molecule of phosphoric acid and thus form adenylic acid. The first two reactions furnish a great deal of energy, whereas the last one is much less efficient insofar as energy production is concerned. The fact that adenylic acid is not found in muscles, except when they have been stimulated to complete exhaustion, indicates that under normal conditions we are concerned only with the breakdown of ATP.

If one were to extract the various materials which have been mentioned previously, and determine the potential heat energy which could be derived from the reactions in their breakdown, the following would represent the energy which might be furnished by one gram of muscle tissue:

Reaction	*Potential Energy from 1.0 Gram of Muscle Tissue*
$ATP \rightarrow ADP + H_3PO_4$	0.04 calories
Phosphagen $\rightarrow$ Creatine + H_3PO_4	0.23 "
Glycogen $\rightarrow$ Lactic acid	1.2 "
Lactic acid + $O_2 \rightarrow CO_2 + H_2O$	30–60 "

From this it appears that ATP is the *initial* limiting source of energy, and, therefore, it must be resynthesized in order that the muscle may continue to function. Thus, one may summarize the anaerobic processes that occur during the contraction of muscle as follows:

$$ATP \rightleftharpoons ADP + H_3PO_4 + \boxed{\text{energy for contraction}}$$

$$\text{Phosphagen} \rightleftharpoons \text{Creatine} + H_3PO_4 + \boxed{\text{energy for resynthesis}}$$

$$\text{Glycogen} \rightleftharpoons \text{Lactic acid} + \boxed{\text{energy for resynthesis}}$$

The reversibility of the last reaction due to the aerobic processes has already been discussed.

In Figure 66, a diagram is used to illustrate the energy relationships in

muscle contraction These reservoirs are shown, each representing a form of energy. "A" is the energy produced by the breakdown of ATP, "B" that produced by phosphocreatine, and "C," that produced by glycogen The energy that escapes from "A" actually starts and keeps the turbine moving

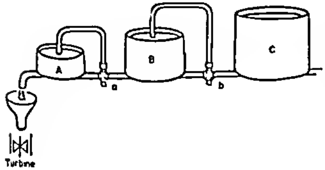


FIGURE 66

Schema for representing the energy relationships between the different processes occurring in muscle during contraction (modified from Lundsgaard) A, reservoir with direct supply of energy (adenosine triphosphoric acid), B, energy (phosphocreatin) added to A when valve a is lowered, C, ultimate source of energy (carbohydrate) flows into B when valve b is lowered

(this is the energy produced by the splitting of ATP). The lever mechanism is so arranged that when the level in "A" has fallen a certain distance the valve between "A" and "B" opens and allows some of the contents from "B" to flow into "A" to make up for the loss (This is comparable to the resynthesis of ATP by the energy produced from phosphagen breakdown) Finally, as the level in "B" decreases the valve between "B" and "C" opens and the contents of "C" flow into "B" "C," therefore, is the ultimate source of all the energy and represents the energy produced by glycogen breakdown Only after this latter source is depleted, does the phosphagen supply begin to disappear (because no energy is formed to cause its resynthesis) Adenylic acid, as such, is found in muscle only after the phosphagen is completely used up and, hence, no energy is available for resynthesis of ATP or ADP, which forms in the absence of phosphagen

THEORIES CONCERNING THE MECHANISM OF MUSCLE CONTRACTION

There have been many theories advanced in an effort to explain the mechanical aspects of the contraction process in muscle Some of them are of historical interest only, others show considerable merit However, none of them are wholly acceptable as such, the matter still being highly controversial

Thermodynamic theories have been prevalent These compare the muscle to a steam engine which transforms the heat produced in oxidation into

mechanical work However, it is known now that the oxidative changes in the muscle fiber occur after, and not before, contraction

A surface tension theory, with a variety of modifications, was for a time widely accepted Usually the attempt was made to link the explanation with that of streaming and amoeboid movements, but, as has been shown for the latter, surface tension at best could explain the movement only partially

An early attempt to interpret the shortening of muscle was based upon elasticity of the fiber or structures contained within the fiber This would, of course, necessitate the existence of the fiber in a condition of tension while in the relaxed state Previously, this sounded highly improbable, but in the light of more recent findings, this principle may actually be involved

The most acceptable theories today are those which explain contraction on the basis of molecular rearrangement The liquid crystal theory, which is illustrated in a simple fashion in Figure 67, is based upon the possible

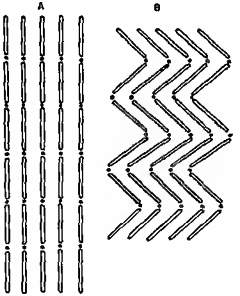


FIGURE 67

Diagrammatic illustration of molecular rearrangement during muscular contraction A molecular arrangement in relaxation or rest B during contraction

existence of rodlike molecules (such as myosin) which could be made to fold on themselves by action of some substance or change within the muscle fibril itself

The reversible gelation theory, which was proposed some years ago, has recently been given considerable support as the result of investigations by Szent Gyorgyi and others It has been discovered that various materials may be extracted from striated muscle If solutions of these materials—the proteins actin and myosin and ATP—are mixed together syneresis

(a shrinking of a gel and consequent loss of fluid from it, such as in a blood clot) will occur when the proper amount of potassium ion is added Other ions also may be important These investigators claim that this may be very similar to the contraction process within the muscle fibril However, difficulty exists because of the fact that the process does not reverse itself in the fashion which might be expected to occur within the tissue In connection with the syneresis process ATP is found to dissociate into ADP and H_3PO_4 and the proteins also undergo changes in combination It is of interest to note that evidence seems to indicate that the breakdown may actually be associated with the conversion of the proteins to their original condition If this is found to be the case then one will have to be content with assigning ATP to a function in the recovery phase of muscle and to continue to look for another means by which the contraction may be initiated

DARK AND PALE STRIATED MUSCLES

It is well known that some striated muscles are much darker than others In some animals such as the rabbit or the chicken muscles of two shades dark (red) and pale (white) can be distinguished even on superficial examination The rabbit has dark breast and pale leg muscles whereas the chicken has pale breast and dark leg muscles The difference is much more extensive than mere shade however they differ in function as well the red muscle contracting slowly and the pale rapidly

Upon microscopic examination the slow red muscles are found to contain large quantities of lipoid substances and appear more granular than the pale When a red muscle is stimulated it is found to have a slow action current as well as slow contraction and relaxation periods If washed free of blood it still retains its opaque red color because of the presence of large quantities of muscle hemoglobin (a respiratory pigment quite different from blood hemoglobin) which is an integral part of the cytoplasm of the muscle A pale muscle on the other hand has a rapid action current and the contraction and relaxation periods are of comparatively short duration This type of muscle is usually translucent and colorless when washed free of blood indicating that there is very little if any muscle hemoglobin present the latter being replaced by cytochrome another respiratory substance There are many muscles that have characteristics which would place them somewhere between the red and the pale Evidently in so called rapid pale muscles of man cat or dog there is some muscle hemoglobin since these muscles have a pinkish color that still remains even after a thorough washing

In many insects such as flies, wasps, and bees, the wing muscles may contract at the rate of 300 times per second The hearts of small birds and mammals (canaries, humming birds, and mice) beat at a rate of from 500 to 700 times per minute when the animal is at rest The muscles used in these rapid contractions contain no muscle hemoglobin, but a large amount of cytochrome

Muscle hemoglobin serves the body chiefly as an oxygen store since it has sufficient storing capacity, can load and unload its oxygen at suitable oxygen pressures, and is able to do this rapidly Further discussion on the function of muscle hemoglobin and cytochrome is taken up later in the section on respiration

UNSTRIATED SMOOTH MUSCLE

At this time it seems desirable to present a few of the salient features of smooth muscles These muscles, as found in humans, have already been discussed briefly, and will be taken up in more detail later when specific organs containing this type of contractile tissue are considered They differ greatly from striated skeletal muscles in many ways, since their origin and development are different This is the type of muscle found in all visceral organs, except the heart—that is organs, such as the stomach, intestines, bladder, uterus, ureter—and the arteries of the body

The smooth muscles respond to the same type of stimuli as do the striated (electrical, chemical, thermal, and mechanical), but are more sensitive to certain chemicals and less sensitive to electrical stimuli The cells consist of relatively short, spindle shaped fibers, which are innervated and controlled by a double set of autonomic nerves As is shown in more detail later, these divisions (*sympathetic* and *parasympathetic*) are antagonistic in their actions, that is, impulses coming over a nerve of one division may cause contraction whereas those coming over a nerve of the other may result in relaxation

Most smooth muscle under suitable conditions exhibits spontaneous rhythmic contraction which appears to be an innate property of the muscle itself These contractions vary in frequency in different organs—from one per minute in the spleen to twelve in the small intestine If smooth muscle is moderately stretched, it will again contract when released

Other distinctive features are marked sluggishness, and the ability to exhibit tonus to a high degree Contraction may take more than 1 min in smooth (stomach of frog) as compared to 0 1 sec in striated muscle (gastrocnemius of frog), mechanical or electrical stimuli may evoke a relaxation when muscle tonus is great, increase in temperature usually causes

a relaxation, as does an increase in hydrogen ion concentration The capacity of smooth muscle for developing any great tension is rather limited

PATHOLOGICAL CONDITIONS OF MUSCLE

Examples of muscular paralysis, a common pathological condition of muscle resulting from nerve injury, are known to all Such muscles are unable to contract normally, and may, with disuse, soon show indications of atrophy Failure of some muscles to contract may prove fatal, thus, after abdominal operations the muscles of the *ileum* (the last 12 ft of the small intestine) occasionally become paralyzed, resulting in intestinal obstruction which may eventually be the indirect cause of death

At times the striated muscles functioning during respiration cannot contract because of injury to their nerve supply—injury such as that caused by infantile paralysis, for example This would be fatal if one did not resort to artificial respiration in the form of an 'iron lung' or the like In this connection it should be noted that the voluntary activity of striated muscle requires the proper functioning of two groups of neurons (nerve cells) One group connects the brain with the spinal cord the other connects the spinal cord with the muscle *Spastic paralysis*, which results in uncontrollable contractions of muscles, is experienced usually when the group of neurons from brain to spinal cord is injured and *flaccid paralysis*, in which there is a limpness of the muscles involved occurs when the group connecting the spinal cord and muscle is injured

Spastic paralysis may be caused by birth injuries to the brain of the infant or it may be produced later in life by other conditions interfering with proper functioning of the motor areas in the brain or the nerve tracts leading down to the cord, such as those attending cerebral hemorrhage or stroke, brain tumors, and other infirmities These injuries apparently affect inhibitory centers and prevent their functioning properly, hence, the lower neurons become overactive, which causes the spastic condition of the muscles

Flaccid paralysis frequently follows infantile paralysis and is the result of injury of nerve trunks as they emerge from the cord or of areas between the cord and muscles which are innervated by these trunks, this condition leads to loss of conduction with the result that the muscles cannot be voluntarily controlled, and consequently become flaccid

Paralyzed muscles if untreated by proper medical methods, such as massaging or moving of the limbs undergo atrophy or degeneration This condition occurs also if the muscle is immobilized by splints or casts, or if a tendon is severed

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Paralyzed muscles if untreated by proper medical methods, such as massaging or moving of the limbs, undergo atrophy or degeneration This condition occurs also if the muscle is immobilized by splints or casts, or if a tendon is severed

In some cases of flaccid paralysis, the possibility exists that the nerve connection may be re-established if damage to the nerve has not been too extensive. The manner of the regeneration of the nerve tissue is considered in Chapter 8. Before the connection between muscle and nerve is again made, however, it is necessary to stimulate the muscle by artificial means in order to prevent atrophy. Thus, the muscle will be in better condition when it may finally be stimulated by normal means—through its nerve.

Muscle may undergo a *spontaneous atrophy*, first evident in the lower limbs, the cause of which is unknown. Deficiency in vitamin E may also lead to atrophy.

Sometimes muscle fibers will contract individually or in small groups only, while the muscle as a whole is quiescent. This phenomenon gives the appearance of quivering and is referred to as *fibrillation*. Evidence seems to support the view that this is caused by a change of conditions within the tissue, and perhaps by an increase in sensitivity to materials found at the ends of nerves and associated with the passage of the impulse from nerve to muscle.

ADDITIONAL READING

Szent-Gyorgyi, A., *Muscular Contraction* (New York: Academic Press, 1951). Newer concepts of muscular contraction.

Part Three

NERVOUS COORDINATION

7

Development of Conductile Systems

IRRITABILITY AND CONDUCTIVITY

As was mentioned previously, irritability and conductivity, fundamental properties of all living protoplasm, are specialized functions of nerve tissue Actually, the properties of irritability and conductivity have been developed in higher animals to a great degree in two types of tissues, muscle as well as nerve, attaining the greatest specialization in the latter It has already been shown that in muscle tissue the property of contractility also is very well developed in highly differentiated forms in lower animals, although to a lesser extent When the nerve of a nerve muscle preparation is stimulated, a contraction of the muscle follows within a very short interval of time Thus, a disturbance which is set up in the nerve by a proper stimulus travels down the nerve (as the impulse) until it reaches the muscle and produces a mechanical effect In this way, the properties of irritability and conductivity highly developed in nerve and muscle tissues, as well as contractility in the muscle, combine in achieving a high degree of coordination

FUNCTION OF THE NERVOUS SYSTEM

The nervous system is a coordinating and adjusting mechanism which is aided in its functions by a complex of receptors (sense organs and the like) usually associated with it

Afferent impulses are those that pass from sense organs to the central nervous system (the spinal cord or brain), and *efferent impulses* those from the cord or brain to the muscle cells or glands

NEED FOR A NERVOUS SYSTEM

In lower animals, there is no need for a highly developed coordinating system, for in most cases the cells are in immediate contact with the environment and thus obtain stimuli directly from it

There is no central nervous system nor any nerve tissue, in the Protozoa or the Porifera, but, nevertheless, they have a means of coordinating and modifying their behavior which, after all, is the main function of such irritable and conductile structures Animals live in a constantly changing

tically all animal phyla have been demonstrated by many investigators According to this definition, most animals, if not all, possess the ability to learn If this is true, we can look for basic phenomena which constitute the function of conductivity in some of the lower organisms *Amoeba* learns to avoid a source of light, although, in most cases, it takes a number of trials before it does so *Stentor*, a ciliate protozoan, modifies its behavior in a number of ways when an unfavorable stimulus is applied to it At first, it merely contracts in order to avoid the stimulus but later may move some distance away from it *Hydra* behaves in a manner quite similar to *Stentor* Its behavior is, however, on a somewhat higher plane than that of *Stentor* but much lower than that of other invertebrates

Such examples are found throughout the animal kingdom but, as organisms increase in complexity, they also progress in their ability to modify their behavior In the *Annelida*, for example, considerable progress is shown over those animals previously mentioned, probably because of their specialized anterior end, and their nervous system, the centralization of which is more pronounced than that in any of the other types The *Arthropoda* are still more advanced in ability to learn Some insects can modify their behavior to the extent of overcoming an inherent pattern in their nervous make up and in this respect are much farther advanced than some of the lower vertebrates Thus, the cockroach by repeated exposure to unfavorable stimuli, may be taught to avoid the darkened environment which it instinctively seeks However, in modifiability of behavior, most vertebrates show considerable advancement over invertebrates, and the mammals especially man, are superior to all others

A study of the development of nervous elements in the various animals mentioned above furnishes information concerning the possible level of behavior in each case

OCCURRENCE OF CONDUCTILE ELEMENTS

Although the *Protozoa* are usually looked upon as forms which show very little differentiation such as is found in the more complex multicellular organisms, there is nevertheless differentiation within the protoplasm itself Yet, these types of cells are not as uniformly conductile and contractile as was once thought It has been found that many of the ciliates exhibit intracellular specialization in that they possess many protoplasmic strands that lead to the cilia from a common center These fibrils along with the cilia are referred to as the ***neuromotor apparatus*** This mechanism described in a preceding chapter (page 51), is illustrated in Figure 68 The center is usually termed the neuromotor center and the fibrils evidently account for the coordination in the beating of the cilia If they are

the space between them which is known as a *synapse*. The conduction is normally in only one direction from one nerve fiber to another. However, a stimulus applied at a point on a nerve fiber is free to travel in any direction along that fiber, until it reaches a synapse. The synapse will then determine if the impulse may pass on to a second neuron.

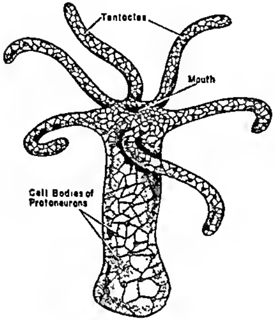

FIGURE 69

The nerve net of the fresh water coelenterate *Hydra*. Note that the proto neurons are continuous so that stimulation at any point results in response of the whole animal.

The earliest occurrence of the nerve-net type of system generally is found in the coelenterates; but similar systems are found also in all of the animals above the coelenterates. Nerve nets are found in the vessels of the human circulatory system; also in the intestinal tract. It is judged to be a primitive type of nervous system for several reasons: (1) it first appears in the coelenterates; (2) in animals above the coelenterates, comparatively speaking, the nerve net is not as important or as extensive as in lower animals; and (3) its structure is very primitive.

Development of Synoptic System from Nerve Net

The nerve net system undoubtedly gave way to the synaptic type of mechanism by gradual development through the ages. Already within the coelenterate phylum we find that changes have taken place in the nervous systems of the various species, from the very primitive type that is structurally and physiologically continuous, to those which are not so ramified but whose fibers appear to lie chiefly in one direction. Under these conditions, the impulse is not so diffuse but travels in the direction

injured or destroyed, the cilia are no longer capable of coordinated movement and the organism moves in a rather erratic manner.

As far as is known, the sponges possess nothing that resembles a nerve mechanism. Each cell, as is true of most living cells, is capable of con-

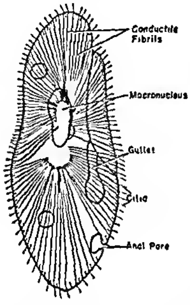

FIGURE 68

The neuro motor apparatus of a ciliated cell, *Paramecium* The conductile elements or fibrils lead from a common center to the cilia and have to do with coordination of ciliary beat

ducting impulses within itself and even conducting from one cell to the next However, the conduction is extremely slow and shows very little resemblance to specialized nerve conduction

the space between them which is known as a *synapse* The conduction is normally in only one direction from one nerve fiber to another However, a stimulus applied at a point on a nerve fiber is free to travel in any direction along that fiber, until it reaches a synapse The synapse will then determine if the impulse may pass on to a second neuron

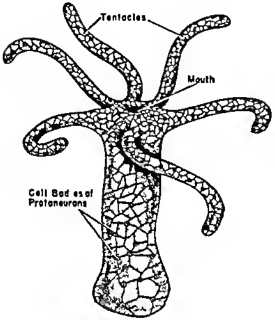

FIGURE 69

The nerve net of the fresh water coelenterate *Hydra* Note that the protoneurons are continuous so that stimulation at any point results in response of the whole animal

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of the longer fibers It is of interest to note that in a nerve net which is stretched, the impulse tends to move in the direction of stretch or tension This evidence gives a clearer view of the development of the synaptic type of nervous system The most highly developed nerve nets show a polarity or a movement of impulses in one direction It is not too illogical to assume that there was, at some period in the development of the nervous system, an actual break between the protoneurons, which resulted in the production of neurons and the space between them, known as the synapse

ACTION OF STRYCHNINE ON NERVOUS SYSTEMS

Interesting observations have been made with strychnine on organisms of the various animal phyla already mentioned This drug has an effect on the nerves at the synapse, increasing the reflex excitability In other words, impulses will spread over almost all synapses in an animal treated with strychnine Thus, in a mammal so treated most of the muscles contract and the glands become more active, resulting in convulsions Consequently, it is obvious that animals with a synaptic type of nervous system will react to strychnine If coelenterates are exposed to its action nothing out of the ordinary happens when they are stimulated, since they have no synaptic system They possess a nerve net, hence the strychnine can make the impulses no more diffuse than they already are If strychnine is injected into the echinoderms, a slight effect is noticed in their responses to stimuli They have both synaptic and nerve net systems, chiefly the latter In the arthropods, the behavior of which is controlled chiefly by a synaptic nervous system, strychnine has a great effect on responses, just as it does on the responses of vertebrate animals

In a general way, one can determine with fair accuracy the dominant type of nervous system possessed by an animal by simply noting its responses *when injected with strychnine*

ADDITIONAL READING

Rogers, C G, *Textbook of Comparative Physiology*, 2nd ed (McGraw Hill 1938), pp 557–614 Nervous coordination in invertebrates

8

Structure and Function of the Neuron

THE NEURON

THE NERVOUS SYSTEMS of man and other vertebrates consist of three parts (1) the central nervous system (2) the peripheral nervous system and (3) the autonomic nervous system (which is discussed later) A diagrammatic indication of the extent of distribution of the main nerve trunks may be obtained from Figure 70 All nerve tissue is composed of cellular units called neurons The neuron is a single nerve cell probably the most highly differentiated of all cells with many protoplasmic processes arising from it

MICROSCOPIC STRUCTURE OF NEURON

In Figure 71 is illustrated the microscopic structure of a single neuron consisting of cell body dendrites axon and end arborization or end brush Two or more neurons may follow one another in succession as will be shown later in the discussion of the reflex arc Always the axon end brush of the one makes contact with the dendrites of the other In the sensory neuron the dendrites (in skin for example) merge into a long fiber which leads to the cell body near the spinal cord This fiber is called a *dendron* The *cell body* a rather irregular structure containing the nucleus (which in turn contains a nucleolus) has an important nutritive function to perform in the life of the neuron The nuclei of cells usually function in division but in the case of nerve cells they no longer have this function hence the cell cannot divide It is evident then that mammals must be born with the same number of nerve cells that they will have throughout life These cells change only in size being very small at birth and becoming much larger in the adult

Usually the fiber of the neuron is thought of as being the part of the nerve concerned with conduction but the cell body must conduct impulses or there would be a block at this point in all cells especially those of the neurons leading to the muscles (motor neurons)

The *dendrites* are fine hairlike structures that lead directly from the cell body They come into close proximity or contact with the axon end

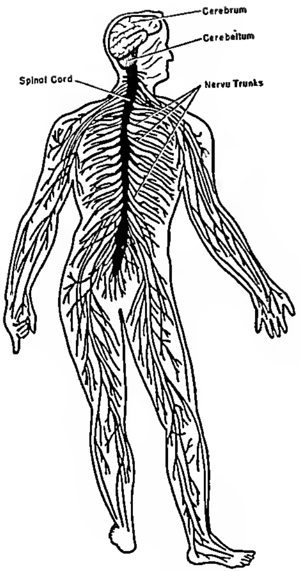


FIGURE 70

Showing extent of main nerve trunks in man.

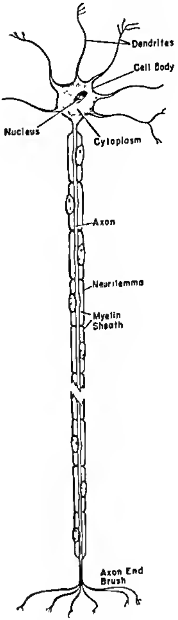


FIGURE 71

A neuron or single nerve cell.

brushes of other neurons. This junction is referred to as the *synapse*. There is actual contact between the end brush of one neuron and the dendrites of another but they are physically distinct structures. The impulse, when it reaches the end brush, must pass over the synapse or functional gap before it can continue over the dendrites and over the axon of the next neuron. Thus, the direction that the impulse may follow over a pathway of two or more neurons is normally controlled by the synapse,

and it may pass only from the end brush of the first neuron to the dendrites of the next one, but not in the opposite direction Some axons are extremely long, especially those of certain motor neurons For example, the axons of neurons in the human sciatic nerve leading to the toes are several feet in length, those of the elephant's sciatic nerve may be as long as 10 ft

CLASSIFICATION OF NEURONS

The structure usually called a "nerve" is properly classified as a nerve trunk consisting of numerous nerve fibers or neurons In the peripheral nerves (or those that lead to or from the surface, the skin or muscle for example), a distinction is made between *sensory* or *afferent* neurons and *motor* or *efferent* neurons The sensory neurons lead from receptors (sense organs, etc) to the spinal cord and the motor neurons from the spinal cord to effectors (muscles and glands) In other words, the nerve trunk is ordinarily a mixed nerve, since it contains the axons of motor neurons and the dendrites of sensory neurons These two types are connected in the spinal cord and brain by *internuncial* or *association* neurons It is by means of these latter neurons that an impulse may be carried to neurons serving various parts of the body (Figure 72, see also Figure 88, page 131)

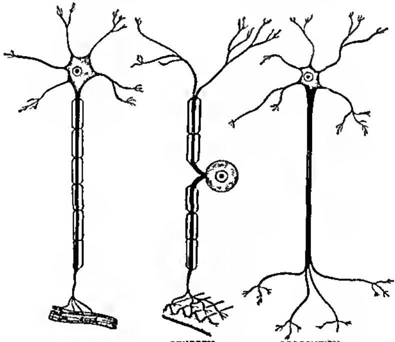


FIGURE 72

Three types of neurons of the central nervous system Only the motor and sensory fibers are medullated

THE MYELIN SHEATH

Nerve fibers may be *medullated* or non*medullated* The medullated fibers are in part enclosed in a myelin sheath covering only the axons which gives the latter a pearly white appearance The dendrites cell body, and end brushes are naked and are therefore gray in color The sheath often regarded as an insulator is interrupted at regular intervals by the so-called *nodes of Ranvier* The whole sheath is enveloped by the neurilemma or nerve membrane Practically all the neurons which enter or make their exit from the central nervous system are medullated Nonmedullated fibers are found chiefly in the autonomic nerves

When a section is made through the spinal cord it is found that the external part of the cord is white in appearance owing to the fact that most of the neurons in this region are medullated The internal portion is gray because the neurons of this area are nonmedullated The position of white and gray matter in the brain is the reverse of that in the cord

STIMULATION OF NERVES

Nerves will react to light and to mechanical thermal, chemical or electrical stimuli that is any rapid change in the physical or chemical condition of the environment will initiate the passage of an impulse over a nerve This passage may be ascertained by means of a galvanometer or by keeping the nerve and its muscle intact and noting whether or not the muscle contracts when the nerve is stimulated

CHRONAXIE OR EXCITATION TIME

Electrical stimulation is much more useful experimentally than other types The effectiveness of the stimulus depends on its intensity as measured by the voltage duration, and rate at which the voltage changes from zero to the intensity of the effective current These factors must be controlled if one wishes to measure the excitability of the nerve In other words the intensity of a stimulus and the rate at which it changes from zero to high intensity or from high intensity to zero are not the only factors involved for it is found that a stimulus of high intensity if applied for too short a period of time may have no effect whereas a much weaker one applied for a longer period of time (but not too long), may produce a response (impulse) The duration of the stimulus is highly important and must be taken into consideration in measurements of this type

The time-duration curve may be obtained by plotting the strength of stimulus (electric current) against the least time needed to stimulate

This is illustrated in Figure 73 in which it is shown that as the strength of stimulus is diminished, it must be continued for a longer time in order to be effective Eventually, the stimulus reaches such a low intensity that it causes no response, regardless of how long it may be continued There

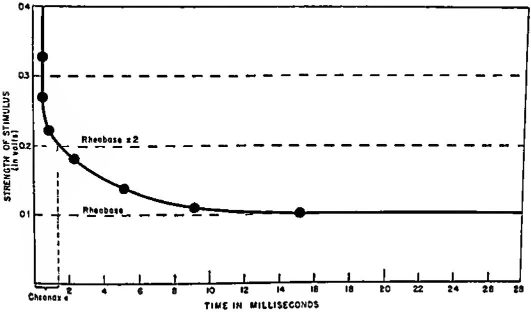


FIGURE 73

The strength duration curve and the manner in which chronaxie is calculated A just perceptible response was obtained for the voltage and time represented by each dot The minimum intensity is the rheobase and a stimulus below this strength no matter how prolonged will not affect the nerve or muscle Chronaxie is the shortest duration of a current necessary for excitation when the current strength is twice the rheobase value

fore, there is a strength of stimulus below which no response may be obtained, although it may be continued for an indefinite period of time This strength of stimulus is called the *rheobase* By doubling the rheobase strength, an intensity is obtained that requires only a very short time to stimulate This is called *chronaxie* and may be defined as *the duration of a stimulus having double the rheobasic value which will produce a perceptible response* It is an indication of the relative reactivity of any tissue Thus the value for chronaxie of nerve is exceedingly short but is longer for striated muscle and longer still for smooth muscle

Polarization at Electrodes

In order to stimulate a nerve or muscle electrically, two electrodes must be placed in contact with the tissue If metal electrodes are used, polariza

tion will take place as it does if the electrodes are placed in a solution containing a salt, such as sodium chloride, that is, positively charged ions will travel to the cathode and negatively charged ions to the anode. Hence, there is an accumulation of positive and negative ions at these poles. These naturally set up a potential difference between the two poles and an electromotive force, opposite to that already acting, is produced—a back electromotive force. The system, therefore, becomes *polarized* and a current no longer flows. In order to overcome polarization during stimulation of a nerve or muscle, *nonpolarizable electrodes* may be used, in which the metal electrodes dip into a solution containing ions of the same metal. For example, if zinc were the metal making up the electrodes, zinc chloride could be used in the solution. When a current is passed through this system, the metal is deposited on the cathode while it gradually goes into solution, freeing ions, at the anode. The latter ions produce a salt by combination with other ions which are migrating towards the anode. This arrangement prevents polarization and the current can continue to flow.

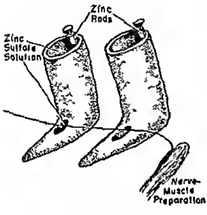


FIGURE 74

One type of nonpolarizable electrode (boot electrodes)

ACTION CURRENT OF NERVE

The action current and evidence that it is really the impulse are discussed in Chapter 5. It is a phenomenon of nerve as well as muscle.

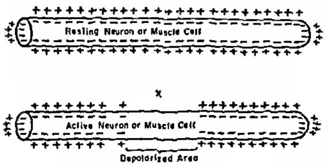


FIGURE 75

Diagram comparing a resting neuron with one that has been stimulated at X

As an impulse or *action current is transmitted over a nerve*, certain changes take place in the nerve. These changes are reversible. There is no mechanical response in nerve but otherwise its physiological activity is similar in many ways to that of muscle. The electrical response has long been

known to be present but thermal and chemical changes have been more recently established

If the electrodes of a very sensitive galvanometer are placed on a nerve, a wave of negativity passes down the nerve each time it is stimulated The wave is very similar to that already discussed under action current in muscle

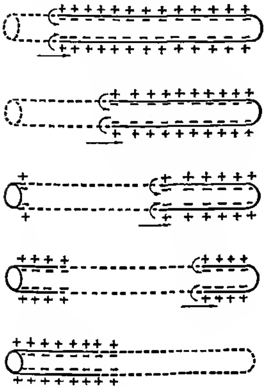


FIGURE 76

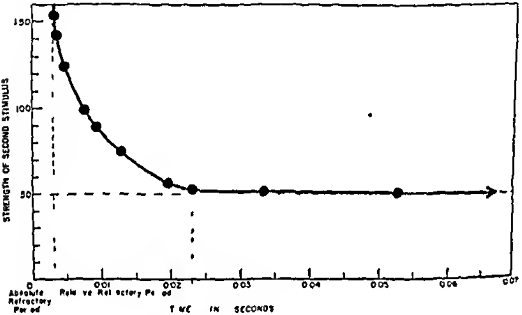
Transmission of impulse over neuron or muscle cell The dotted regions indicate a depolarized condition and an increased membrane permeability which permits a movement of ions as shown by the curved arrows This is the impulse that progresses over the nerve or muscle cell and is followed by the recovery phase (modified from Carlson and Johnson)

The impulse may travel in either direction along a nerve fiber, as is evident when a nerve branch or nerve trunk (such as the sciatic) is stimulated Only the synapse will govern the continuation of the impulse over a series of neurons, as mentioned previously The galvanometer can detect current moving in either direction along the axons and dendrons away from the point of stimulation

REFRACTORY PERIOD

Immediately following stimulation of a nerve, there is a very short period of time referred to as the *refractory period* when it is no longer sensitive to further stimulation A situation or condition exists which is quite similar to that found in muscle during its refractory phase As in the latter case there is an *absolute refractory period,* when the nerve will not respond to a second stimulus no matter how intense it may be, and a *relative refractory*

period, when a sufficiently strong stimulus may evoke a second response In other words, during the relative refractory period, the nerve is beginning to recover (repolarize) Naturally, during the time immediately following the absolute refractory period it has recovered only slightly, hence, it would require a stimulus of great intensity to cause an impulse to flow at that time However, when the nerve has almost entirely repolarized it requires a stimulus only slightly greater than threshold (minimal) to elicit a response The recovery of nerve after stimulation and the variations in refractory periods are well illustrated in Figure 77



in irregular short lengths The myelin sheath, just beneath the neurilemma, breaks up into droplets of variable size which later undergo chemical changes The neurilemma remains intact, at least for some time In certain nerves, regeneration may take place This is first noticed as a growth of the neurofibrils from that part of the axis cylinder that has not undergone degeneration The regenerated fibrils follow the pathways of the degenerated part of the neuron provided the neurilemma is still present It is believed that the neurofibrils are able to do this by means of a chemotactic response, that is, that there is a chemical attraction for them in the old pathway They may regenerate at the rate of 0 5 to 2 mm per day The neurilemma is absolutely essential for this activity and, therefore, nerves that do not have this membrane do not regenerate Thus, if the nerves in the spinal cord or, for instance, those of the eye or ear, are severed, loss of movement and/or sensation is permanent, since in these as well as in other nerves the neurilemma is lacking If a wound is severe enough to cause too great a gap between the undegenerated and degenerated track, the regenerating ends of the fibrils may not find their old pathways Under these circumstances they sometimes continue to grow and produce a tangled mass called a *neuroma*, which may be quite painful because of the pressure This explains the painful sensations that appear to exist in the toes of a person whose leg has been amputated The pressure brought to bear on the ends of the sensory neurons that formerly led from the toes initiates impulses that are carried to the brain

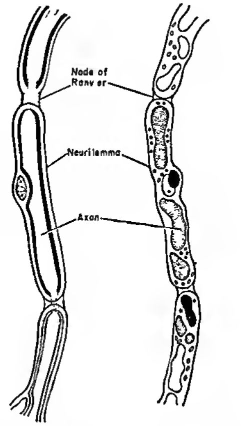


FIGURE 78

Comparison of normal neuron with one showing Wallerian degeneration

SPEED OF CONDUCTION

Before 1852, it was generally believed that the nerve impulse traveled at a rate equal to that of light which is about 186 000 miles per second At this

time, however, the great German physiologist, Helmholtz, reported the results of an ingenious experiment which proved definitely that the speed of the nerve impulse was only 30 meters per second in the frog gastrocnemius or slightly more than 1 mile per minute The speed of the nerve impulse in the frog is, therefore, a mere fraction of that of light or electricity By modifying his methods somewhat and using the gastrocnemius muscle of the frog with the full length of its sciatic nerve attached records may be obtained on a rapidly moving drum of a kymograph from which can be calculated the speed of the nerve impulse The arrangement is illustrated in Figure 79 Although rather crude, this method gives surprisingly accurate results

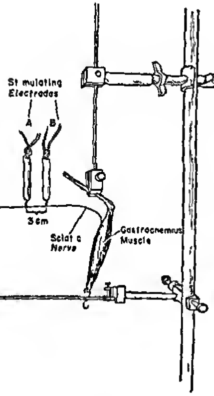


FIGURE 79

Diagram of the apparatus for ascertaining time of nerve impulse according to Helmholtz Records were obtained for the contraction of the muscle when stimulated first by electrodes A and then by electrodes B The difference in the latent periods is the time it takes for the impulse to travel the 3 cm of nerve between the two pairs of electrodes

Two pairs of electrodes are applied to the nerve one at the upper end and the other as near the muscle as possible Records may now be taken of the contraction of the muscle when its nerve is stimulated first at the near electrode and then at the more distant one The exact time the stimulus is applied is noted and a time scale produced as indicated in Figure 80 It is found that the latent period is shorter in the first case than in the second and the difference between these two periods gives the time the impulse has taken to pass over that portion of the nerve between the two electrodes Knowing the distance (3 cm) between the two electrodes and the time (1

millisec) the impulse takes to travel this distance, it can be calculated that in 1 sec the impulse will travel 3000 cm , or 30 meters This is the figure obtained by Helmholtz which was later proved to be fairly accurate although it would be very difficult to ascertain much greater speeds by such a method

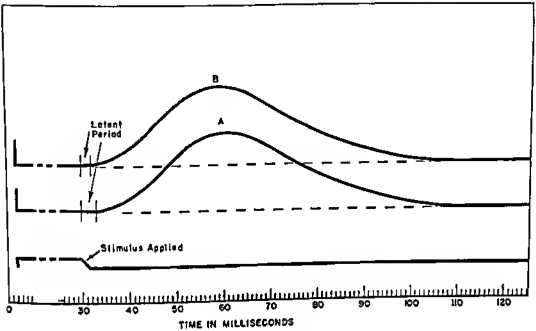


FIGURE 80

Copy of records obtained when a nerve muscle preparation is stimulated as described in Figure 79 The latent period before the muscle contracted when the nerve was stimulated by the second pair of electrodes (curve A) was one millisecond longer than that produced when the first electrodes were used (curve B) In other words it took the impulse 1 millisecond to travel over 3 cm of nerve

MODERN METHODS OF ASCERTAINING SPEED OF IMPULSE

More modern methods now employ the cathode ray oscillograph with which the speeds of nerve impulses can be determined much more accurately Gasser and Erlanger who perfected this method (1922–1929) found that the speed of impulses over the nerves of mammals was in some instances greater than 100 meters per second but they also found that in some nerves the speeds were even less than those in the frog sciatic nerve In fact, by using the oscillograph and by comparing nerve fibers in cross sections of sciatic nerves these investigators conclude that there are at least five different types of nerve fibers in the sciatic nerve four of which can be distinguished structurally Thus as shown in Figure 81 the medullated fibers may be placed in three groups—large medium and small—the size depend

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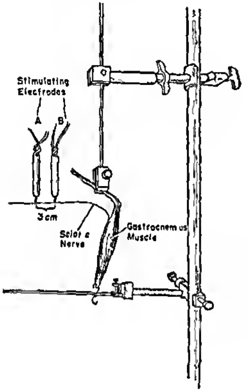

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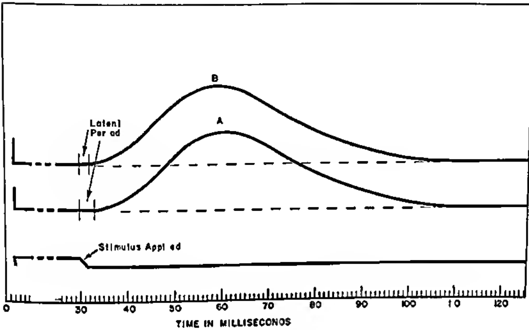

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ing upon the thickness of the sheath The largest consist of both motor and sensory fibers and the impulse is propagated over them most rapidly—up to 120 meters per second The medium and small fibers are sensory and conduct at rates from 30 to as low as 14 meters per second

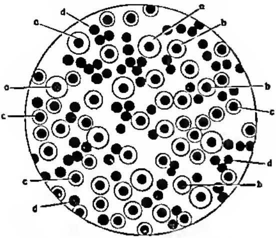

FIGURE 81

Diagram of a cross section of the sciatic nerve showing various types of fibers a large thick medullated fibers b less thickly medullated fibers c least medullated fibers d nonmedullated fibers

The nonmedullated fibers consist of those that transmit the impulse at a rate of from 11 to 17 meters per second and those that transmit it at 0 3 to 1 5 meters per second

ALL OR NONE NATURE OF THE NERVE IMPULSE

There was a time when it was believed that the nerve impulse depended entirely upon the intensity of the stimulus If this were true, the intensity of the action current passing over a nerve would vary with that of the stimulus However as discussed in Chapter 5 in connection with striated muscle, there is a threshold value for the stimulus of proper duration If the latter has an intensity below the necessary threshold, nothing happens, it does not excite the neuron If the intensity of the stimulus is above this value it has no greater effect than the threshold stimulus itself If galvanometer electrodes are placed at various points along a nerve (such as the sciatic) and a stimulus of threshold value is applied to it, it is found that the intensity of the action current is the same all along the fiber Another interesting fact is that the impulse may decrease in intensity while passing over a portion of a nerve that has been narcotized, but will regain its full intensity again after reaching the nonnarcotized part Added up, these facts simply mean that in order for a stimulus to excite neurons, it must produce at least a minimal change at the point applied and once the stimulus accomplishes this, a propagated response is set up along the fiber which is of maxi

mal intensity. In other words when a stimulus is applied to a neuron (or muscle cell) it results in a maximal response of these cells or none at all, thus, the neuron follows the all or none law. This is of value to the animal in that it would otherwise respond unnecessarily to too many stimuli.

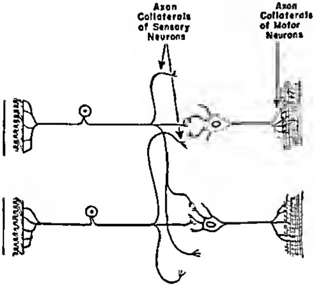

FIGURE 82

Illustrating the manner in which different sensory neurons can carry impulses to the same or different muscle units by way of axon collaterals. The synapse is found within the spinal cord.

Axons are subdivided into many collaterals, so that an impulse traveling from the cell body of a motor neuron will pass over many collaterals in order to affect many muscle cells. It does not decrease in intensity as it passes over these various collaterals but retains its original intensity in all the branches—another manifestation of the all or none law.

METABOLISM OF NERVE

Heat Production in Nerve

During activity of nerve, that is, when the impulse passes over the nerve heat is evolved, but the amount is hardly detectable and was unmeasurable until 1926, when extremely sensitive thermopiles were produced. The number of thermal junctions in the thermopiles used for detection of heat in nerve had to be increased greatly. It has been found that the heat phases during the passage of the impulse are approximately the same as those during contraction of muscle. Two phases have been indicated: (1) initial heat, (2) recovery heat. Even when the nerve is resting some heat is given off and can be detected. It increases greatly when the nerve is stimulated.

The initial heat is small in amount and disappears as soon as stimulation ceases. The recovery heat can be further divided into two phases: the early rapid phase which corresponds to that of the initial heat, and a prolonged

phase the extent of which depends upon the duration of the stimulus. The duration and amount of heat produced during the two phases are shown in the graph of Figure 83. The nerve in this case had been stimulated at the

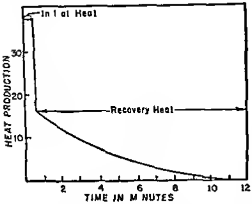

FIGURE 83

Graph illustrating the initial heat produced (in arbitrary units) as compared to the recovery heat (after Bronk). Stimuli given at the rate of 140 per second for 30 seconds. The initial heat is produced only during the period of stimulation.

rate of 140 stimuli per second for 15 sec, heat continued to appear for 10 min after stimulation had ceased. The initial heat makes up less than 10 per cent of the total heat produced. It is impossible with present day methods to ascertain the heat produced by a single nerve impulse; that is why a volley or series of impulses must be given to obtain results such as those presented in Figure 83. However, it has been calculated that a single impulse may raise the temperature of a nerve about one millionth of a degree C. Thus the initial heat phase would be equal to one ten millionth of a degree or less.

CHEMICAL CHANGES AND THE NERVE IMPULSE

It is more difficult to link up heat production and chemical processes involved in impulse flow in nerve than it is in muscle contraction. Chiefly because of the difficulty in ascertaining the changes that take place in nerve, it was not until 1933 that respiration (oxygen consumption and carbon dioxide elimination) was first determined. Gerard and Hartline used a rather simple micro-respirometer, the basic principle of which is illustrated and described in Figure 84. The eye of the king or horseshoe crab (*Limulus*) with its attached nerve was used in their experiments. The nerve is placed in the tube the end of which is sealed off with vaseline. The other end of the

tube is sealed by means of a drop of sodium hydroxide solution Two pieces of filter paper are placed inside the tube, the one, saturated with sulfuric acid (to absorb ammonia which is produced by active nerve), and the other with sodium hydroxide (to absorb carbon dioxide) Thus, any movement of the droplet (the temperature and pressure being constant) indicates utilization of oxygen and if the diameter of the tube is known, the actual amount of the gas eliminated can be calculated The nerve becomes active as soon as the attached eye is exposed to light The evidence indicates a long recovery period in nervous activity

NATURE OF THE NERVE IMPULSE

What is the significance of all of these phenomena associated with the nerve impulse? It is said that the nerve membrane is normally *polarized* when at rest in that a positive charge exists on its external and a negative charge on its internal side, one charge potentially balancing the other According to the theory of nerve conduction, the ions are free to pass through the membrane when a stimulus is applied In experimental procedures, it is most convenient to apply an electrical stimulus This results in an immediate *depolarization*, since the ions, which were oriented on opposite sides of the membrane, are free to move together However, merely striking the nerve with a hard object causes local injury and depolarization may occur as a result There is evidence to indicate that cations, on the outer surface of the membrane, may pass inward to unite with anions on the inside Now, when this local depolarization occurs, that area and the polarized area immediately adjacent, act as a battery and there is a flow of ions from the outside to the inside resulting in depolarization of that portion of the membrane This procedure, repeated along the length of the nerve, is *self-propagating* and is the nerve impulse It evidently requires very little expenditure of energy and may occur in the absence of oxygen

During repolarization or recovery, when the ions are separated and the membrane again becomes impermeable to them, energy is required The refractory period exists because of the time it takes under normal conditions to restore the nerve to its polarized conditon after depolarization While considerable energy may be furnished by anaerobic processes, eventually oxygen will be required for complete recovery just as is the case in muscle This is the reason why a nerve that is stimulated repeatedly in the absence of oxygen loses its excitability It fails to recover, although this condition is reached only after periods of stimulation up to three hours If the nerve is now exposed to oxygen its former condition may be restored

The actual chemical processes involved in conduction of impulses are

not entirely known In some respects energy is furnished in a manner similar to those processes involved in muscle contraction There is a breakdown of creatine phosphate and adenosinetriphosphate This latter material may serve as an eventual source of ammonia, which is produced during metabolic activity in nerves, a process *different from that in muscle* Carbohydrate metabolism has been difficult to demonstrate, although in pathological conditions, that is, beriberi, owing to a lack of thiamine or vitamin B_1 end products of incomplete carbohydrate metabolism accumulate in nerve tissue Under normal conditions, the final utilization of these substances may be an important phase in furnishing energy for maintenance of polarity of the nerve membrane

Von Muralt (1937) claimed that the rapidly reversible production and destruction of acetylcholine, which had previously been shown to be associated with conduction of the impulse across the motor end plate, was an important event in the conduction of the impulse More recently, Nachmansohn (1945) has extended this theory and shown that the metabolism of acetylcholine is closely linked to the breakdown and resynthesis of adenosinetriphosphate Thus, it appears that the chemical processes involved in muscle and nerve may be closely related in many respects

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Heilbrunn L V An Outline of General Physiology 3rd ed (Saunders, 1952) ch 37 Conduction

Nachmansohn D On the Role of Acetylcholine in the Mechanism of Nerve Activity, *Vitamins and Hormones* 3 134 1945

Rosenblueth A, *Transmission of Nerve Impulses at Neuroeffector Junctions and Peripheral Synapses* (Technology Press of the Massachusetts Institute of Technology and John Wiley, 1950) Chemical mediation of nerve impulses

9

The Spinal Reflex System

GROSS STRUCTURE

THE SPINAL REFLEX SYSTEM is dependent upon the spinal cord and spinal nerves that lead to and from the periphery or outer portions of the body (muscles glands and sense organs), hence the use of the term peripheral nerves as synonymous with spinal nerves This discussion will be concerned with the peripheral or spinal nerves (because they lead to or from the cord) and the spinal cord The cranial nerves, which lead directly to and from the brain, will be considered in a later chapter In order for the cord to be examined, the backbone which protects it must be cut away The backbone itself consists of thirty three vertebrae These are essentially ringlike in form, with transverse projections and spinous processes (Figure 24 page 41) to which are attached muscles by means of tendons which make the back bone strong but flexible

The cord is a continuation of the brain there is no sharp line denoting the end of brain tissue and the beginning of the spinal cord The latter, in adult humans, continues to the lower edge of the first lumbar vertebra, whereas in fetal life it extends to the very end of the canal The lower part of the adult spinal canal contains a mass of nerve trunks known as the *cauda equina* (meaning 'horse tail which it resembles) As previously mentioned, the cord has a pearly white appearance externally but in cross section reveals the presence of gray matter which indicates that the nerve tissue in the central portion is unmyelinated

CROSS SECTION OF CORD

It is evident in the diagram of the cross section of the spinal cord that each spinal nerve just before it appears to enter the cord divides into two roots one enters the back of the cord and is called the *dorsal root*, the other appears to enter from in front and is called the *ventral root* Just before

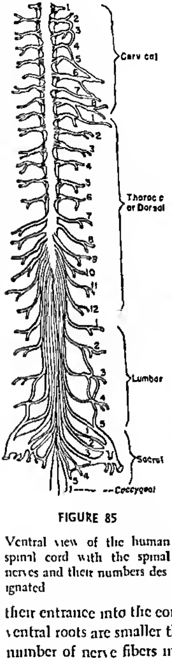

FIGURE 85

Ventral view of the human spinal cord with the spinal nerves and their numbers designated

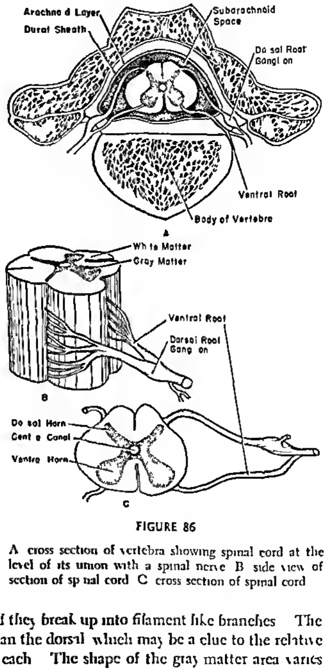

FIGURE 86

A cross section of vertebra showing spinal cord at the level of its union with a spinal nerve B side view of section of spinal cord C cross section of spinal cord

their entrance into the cord they break up into filament like branches The ventral roots are smaller than the dorsal which may be a clue to the relative number of nerve fibers in each The shape of the gray matter area varies

from one level to the next but, on the whole, it has the shape of the letter "H" or a pair of butterfly wings. The area in the extreme dorsal portion of the cord is called the dorsal horn, that in the ventral portion, the ventral horn. The cord is enlarged in the cervical and lumbar regions, the diameter is noticeably greater in the cross sections taken at these levels. It is enclosed entirely by connective tissue membranes similar to those found enveloping the brain. These membranes protect the cord from the twisting and bending movements to which the backbone is subjected. Cerebrospinal fluid is found in the space between the membranes and the cord.

The neurons of the ventral roots all have their cell bodies in the ventral horn whereas the cell bodies of those entering the cord by way of the dorsal root are located in the spinal ganglia. Before the nineteenth century, nothing was known concerning the functions of these roots, although the concept of reflex action had already been advanced by Descartes (1649). He postulated that impulses originating at the receptors on the body surface pass to the central nervous system where they are "reflected" back to muscles or glands which then respond mechanically resembling the manner of the reflection of light by a mirror. The structures involved in this "reflection" were said to make up the *reflex arc* (Figure 88).

The Roman physician, Galen, who lived in the second century A.D., understood that the peripheral nerves were of two types. He said, "there are nerves to the muscles and others to the skin; when the former are affected, movement is abolished, when the latter, sensibility." He, thus, definitely distinguished between what are now known as motor (efferent) and sensory (afferent) neurons. The next question was whether they enter and leave the cord separately or together. The first actual experimentation on the spinal roots was made by Charles Bell, an Englishman, in 1811. He demonstrated that the ventral roots contain motor (efferent) nerves. Ten years later, Magendie proved that cutaneous sensibility is lost in certain regions when the dorsal roots are severed whereas it is unimpaired when the ventral roots are cut.

These observations resulted in the appearance of the Bell-Magendie law: sensory impulses enter the cord via dorsal roots whereas motor impulses leave via ventral roots. Therefore, ventral roots contain only fibers of motor neurons whereas dorsal roots contain only fibers of sensory neurons. The demonstration of this law is illustrated in Figure 87. The experiment may be readily repeated by exposing the spinal cord of a large bullfrog and cutting the dorsal roots on one side of the cord leaving the ventral roots on that side intact and cutting the ventral roots on the opposite side of the cord. If the

peripheral stumps of the ventral roots are stimulated the muscle or muscles innervated by that root contract Stimulation of the central stump produces no mechanical response whatever

If the peripheral stumps of the cut dorsal roots are stimulated there is no apparent response but if the central stumps are stimulated signs of pain

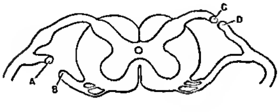

FIGURE 87

Demonstration of the Bell Magendie law On the left side the ventral root is cut stimulation at A causes contraction of muscles to which the nerves lead stimulation at B results in no evident response On the right side the dorsal root is cut stimulation at C causes contraction of muscles while stimulation at D produces no response It is therefore evident that the dorsal root carries *sensory neurons (impulses to the cord)* and the ventral root carries motor neurons (impulses away from the cord)

are obtained as well as muscular contraction (if ventral roots are intact) After cutting all of the dorsal roots containing nerves that innervate the receptors of the area involved the area is found to be wholly insensitive to any stimulus

REFLEX ACTION

A reflex may be defined simply as an unconscious response to a stimulus The initiation of the impulse by the stimulus and its passage over the neurons to the structure (muscles) which respond is referred to as *reflex action* The *reflex arc* consists of the structures over which the impulse passes

The application of stimuli to various parts of the body surface produces responses in animals A stimulus is any environmental change that produces a response *Most responses may be classified as trigger reactions* The energy of the stimulus is extremely small compared with the energy output represented in the response to that stimulus just as the energy applied to the trigger of a gun is very small compared with the energy of the explosion which follows The organism is able to adjust itself to its environment in this way

Reflexes may be grouped into three classes (1) *simple reflexes* in which a single muscle is affected (such as the muscle concerned in winking) (2) *co*

ordinated reflexes in which many muscles respond, but in such a way as to bring about orderly behavior in an animal (3) *convulsive reflexes* in which many or even all the muscles contract in an uncoordinated way This occurs after the injection of strychnine Reflex activity is shown also by glands, smooth muscle, and cardiac muscle, this depends upon the autonomic nervous system, however, and is discussed later

A rather simple example of the workings of an adjustive mechanism in humans is shown by the sequence of events which follows when a finger accidentally touches a hot object These events (which include the components of a reflex arc) are as follows

1 The skin receptors are stimulated by heat
2 The resulting impulses are carried over sensory neurons to the spinal cord
3 Almost instantaneously the impulses are here passed over to motor neurons at the same level in the cord This may occur either directly or via the association neuron
4 The motor neurons convey the impulses to the muscles which move the arm
5 The muscles contract and move the arm thereby drawing the finger away from the hot object

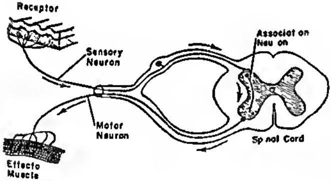

FIGURE 88

The reflex arc The stimulus at the receptor produces an impulse which is carried to the cord by the sensory neuron across the association neuron and back to the effector by way of the motor neuron

All of these processes go on in an individual whose spinal cord has been separated from the brain In other words consciousness is unnecessary the processes occur in its absence Such a sequence constitutes a reflex arc and it has at least four and usually five components These are receptor sensory or afferent neuron association neuron (this may or may not be included), motor or efferent neuron and effector The time involved from the moment of application of the stimulus to the beginning of the reaction is known as the *reflex time* (or reaction time)

SPREADING OR IRRADIATION OF REFLEXES

There are two ways in which spreading or irradiation of reflex impulses may be brought about (1) by the use of strychnine which affects the synapses in

the cord (this has already been discussed), or (2) by increasing the intensity of the stimulus, thus affecting more of the sensory neurons

If the hind foot of a spinal frog (one in which the brain has been destroyed) is stimulated by means of a current of low intensity, the animal will respond simply by withdrawing the foot If the stimulus is an intense one, not only is the foot jerked away, but the muscles of the opposite leg and foot contract also Even the muscles of the forelegs and trunk may show activity This experiment indicates that the impulses which had passed over the sensory nerve from the foot to the cord are transferred to association neurons within the cord, which pass to the opposite side and make synapse with the motor neurons there as well as with motor neurons on the same side This is not all, however, for some of the impulses may be carried by way of other association neurons, to higher or lower levels in the cord

CONDUCTION IN THE CORD

The segmental arrangement of the central cord in the lower animals (especially invertebrates) is obvious, also, it is primitive in that each ganglion regulates the activity of the segment in which it lies It has already been noted that in the spinal cord of man the thirty one pairs of spinal nerves designate a segmentation (metamerism) by their arrangement along the cord However, although some simple spinal reflexes may be controlled by a particular segment or segments, it is found that, for the most part, the reflexes are more closely correlated than this, and that control over the general behavior of an animal is centered in the brain This means that the spinal cord must have within it conducting pathways to and from various levels in the cord as well as pathways to and from the higher centers in the brain These pathways are found in the white matter which contains both motor and sensory fibers The fibers are medullated but evidently possess no neurilemma and are contained within tubes which are formed by the surrounding tissue On each side of the spinal cord (which is divided by the dorsal and ventral fissures—indentations or depressions) there are three main columns or *funiculi* (Figure 89) (1) one between the ventral fissure and the ventral horn, (2) one lateral to the gray matter and (3) one between the dorsal fissure and the dorsal horn

NERVE TRACTS

The spinal nerve tracts (*fasiculi*) containing nerves that carry impulses to and from the brain, are located within the main columns or funiculi of the cord The white matter of the cord decreases progressively towards the tip This, naturally, would be expected because there are neuron fibers entering

and leaving the cord at all levels to make synapses with fibers in the tracts The size of the fasciculi therefore is increased at every level in the cord so that by the time the uppermost levels of the cord are reached there are many more ascending and descending fibers Some of the fibers of the tracts function chiefly within the cord itself in regulating and correlating the spinal reflexes Therefore, they do not go all the way up the cord or all the way down, but may be so arranged as to take over impulses from sensory neurons at one level of the cord and give them up to motor neurons at another level Hence the amount of white matter at the level of the cord where it joins with the medulla is not as great as it would be if all the fibers in all the tracts entered or left the brain One of the tracts that is described later is the

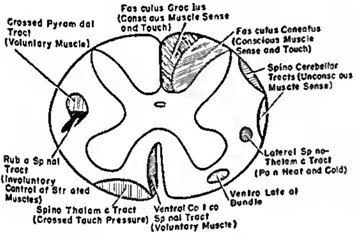

FIGURE 89

Cross section of spinal cord showing the positions of some sensory or ascending and of some motor or descending tracts

pyramidal tract (descending) which originates in the motor cortex of the cerebrum Other tracts are indicated in the areas shown in the diagram in Figure 89 Most of the unlabeled area contains fibers or tracts that never enter or leave the brain but are contained entirely within the cord

A great deal of information concerning these pathways has been gained by sectioning the cord and its nerves at various levels, as well as by observing the behavior of persons with injuries to the spinal cord

If a spinal nerve trunk is severed, sensation and motor functions are permanently lost in the region supplied by the nerve The results of cutting through the dorsal or ventral root of the spinal nerve have already been discussed (page 130)

If the spinal cord is cut completely across, the animal goes into *spinal shock* lasting a few minutes to several hours, or even days it lasts longest of all in mammals—man especially—although even in humans the shock gradually disappears During shock all sensation muscular action and

reflexes are lost in the area which was innervated by the nerves of the cord below the cut. Naturally, because of the fact that the brain connections are severed sensation is permanently lost in the area mentioned above as is the ability to contract the muscles voluntarily. However, many of the spinal reflexes reappear after the symptoms of shock have disappeared.

INHERENT PATHWAYS

Animals have inherent patterns within their nervous systems which determine to a limited degree the pathways that each particular impulse will follow. A stimulus applied to a receptor will almost always arouse the same reflex response, although this does not mean that there is only one pathway open to impulses coming over each sensory neuron, that is, these pathways are not rigidly fixed. If they were, there would be no spreading of reflexes, and an animal would be unable to protect itself fully. The application of a stimulus to the human eye furnishes a good illustration of this: if a small particle is carried in the air towards a person's eye he may wink, if a large object such as an insect approaches the same eye, he may turn his head to one side; if the object should happen to be a stone, he would probably dodge by bending the upper part of the body to one side. The impulses travel in every case over the same sensory nerve, the optic nerve. Thus, it is obvious that the sensory neurons of the optic nerve do not necessarily pass all of their impulses to the same group of motor neurons such as the one that leads to the eye muscles used in winking. Actually, these impulses may proceed over many association and other motor fibers and may finally terminate in muscles far distant from the eye. This is true of the nervous system as a whole: there are so many possible connections among all the neurons that impulses flowing over any sensory neuron may ultimately proceed over any motor neuron. The fact that they do not usually do this is due to the presence of the innate pathways that are usually open to certain impulses; that is, certain dendrites are more accessible to the end brush of certain neurons than others. However, if the impulses are numerous enough, they may pass over to the dendrites of motor neurons that are not so accessible.

SUMMATION, FACILITATION AND INHIBITION OF REFLEXES

Many times a *summation* of stimuli seems to be the most favorable method of starting a reflex response, that is, many subminimal stimuli applied to a receptor may be effective, whereas a single strong stimulus may not be. The subject of summation of subminimal stimuli has already been touched upon in the discussion of muscle action.

It is thought that a substance is produced at the tips or synapses of the

nerve endings (see autonomic system) which transmits the excitatory process across the synapse Summation of stimuli, then simply means that whereas with one stimulus, an insufficient quantity of the substance (for example, acetylcholine) is produced, on the other hand with many rapidly repeated stimuli, a large enough quantity is formed to elicit the response

When one stimulus results in a rather weak response, this response may be strengthened by the simultaneous application of an entirely different stimulus For example, a much greater response is obtained with the knee jerk if the subject at the same time is subjected to another stimulus, such as clenching his fist, hearing a loud noise, reading a newspaper, or a similar action The term *facilitation* or *reinforcement* may be used for this phenomenon

Reflexes can be inhibited voluntarily (cerebral inhibition) Also, they are sometimes inhibited by *simultaneous afferent impulses* For example, sneezing can often be prevented by applying pressure to the upper lip or by rubbing the nose If the irritability of the nervous system as a whole is decreased as during sleep or narcosis, reflexes are inhibited and abolished The abdominal and patellar reflexes are the first to disappear under these conditions, the corneal and retinal are the last to vanish

FATIGUE

Nerve axons are practically immune to fatigue It is impossible to fatigue them if they are receiving their proper oxygen and food supply by way of the blood stream On the other hand it is found that reflex responses are very susceptible to fatigue It should be kept in mind that in dealing with reflex arc constituents the cell bodies of the nerves must be considered as well as the axons The former have a much greater metabolic rate than the latter which may, at least partly, explain the onset of fatigue It has been found that fatigue first appears in the spinal cord and since it is known that the axons themselves do not fatigue it probably occurs at the synapse Evidently, the resistance at the synapse is increased as more and more impulses travel over it until finally the resistance is too great for the impulses to pass Perhaps there is no longer production of acetylcholine at the tips of the axons, this would prevent the passage of the impulse over the synapse if it depends upon chemical mediation or transmission (page 178)

AFTER DISCHARGE

Impulses, which result in muscle contractions, may continue to cause contractions long after the stimulus has ceased this continued discharge of impulses is called *after discharge*

It has been pointed out that most, if not all, muscle contractions are tetanic contractions and not single contractions. That is, when an arm is raised it is done by means of many muscles contracting simultaneously, but it is a smooth, steady contraction and relaxation which can be accomplished only by the reception of many impulses (volleys of impulses) in the muscles. Reflex responses are brought about by volleys of impulses causing contractions that may last several seconds, followed by a gradual relaxation which also may take several seconds. For example, when the finger is pricked with a pin, the *series of* contractions necessary *to pull the* hand *away from the* source of stimulation continues long after the stimulation has ceased. In other words, a single stimulation applied to a receptor causes an impulse (or a single volley of impulses) to pass over the sensory neurons. The motor neurons which lead from the sensory neurons may continue to discharge impulses for some time after the original stimulus or, much more likely, in the central nervous system, the motor neurons are stimulated by impulses arriving from sensory neurons in a sort of closed ring circuit arrangement as shown in Figure 90. This continued activity of the motor nerves after the stimulus has been removed is referred to as *after discharge*.

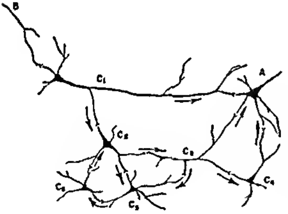

FIGURE 90

The hypothetical closed ring circuit which might account for after discharge of impulses from the motor nerve A which would receive stimuli from the sensory nerve B through interneurons of the chain C_1 C_2 C_3 C_4 C_5 C_6

SPINAL REFLEXES IN MAMMALS

The spinal cord has two main functions: (1) it acts as a reflex center, and (2) it conducts impulses to and from the brain and thus, is instrumental in correlating the actions of the peripheral structures with those of the cerebrum and other parts of the brain.

In order to study spinal reflexes experimentally, the brain of an animal may be removed. Such an animal is called a *spinal animal* and is prepared by severing the spinal cord from the brain just behind the medulla. In this

way disturbing factors from the higher nerve centers are removed If a mammal is used such as a dog or cat it can be decapitated under anesthesia if great care is taken to tie off the blood vessels As mentioned previously, the more complex the animal used the more difficult it is to keep it alive under these conditions Respiration ceases immediately on severing of the spinal cord at this point because the centers that control respiratory movements are in the medulla The temperature regulatory centers are in the thalamus so that the spinal mammal actually becomes a poikilotherm (cold blooded) However if proper artificial respiration and warmth are applied it can be kept alive for a period varying from several hours to several days The blood pressure falls immediately after the operation and many of the spinal reflexes are abolished a condition existing in spinal shock (page 152) but return after a few hours Although the blood pressure never again reaches normal it is sufficient to maintain an adequate supply of blood for the tissues especially for the cord

In a dog which has undergone such a radical operation the action of several reflexes can be readily observed Three well known spinal reflexes can be demonstrated if the body of the dog is placed in a position that allows the limbs to hang free This can be done by strapping it to a plank held high enough to allow free movement of the legs

Flexor Reflex

When skin receptors of touch temperature or pain are stimulated over a wide area of a limb the resulting withdrawal of the limb from the stimulus is known as a *flexor reflex*

If the toe of one of the limbs of the spinal dog is stimulated (pinching pricking with needle or the like) the limb is drawn away after a brief latent period In nature this is a protective reflex in that it causes various muscles of the thigh and lower leg to contract and in this way flex the limb to draw it away from danger or painful stimulation The latent period of all reflexes is long compared with the time required to pass over the nerve axon alone This is owing to the fact that the impulse travels comparatively slowly over the synapse In a reflex arc then the latent period is the time consumed by the impulse in traveling over all the nerve fibers involved and in passing over the synapses in the spinal cord

The Scratch Reflex

Everyone who has patted or scratched a dog on its side has observed the scratch reflex The hind leg on the side stimulated begins to produce scratching movements that are fairly accurate in locating the area patted

This accuracy might lead one to believe that the scratching is voluntary This is not the case, however, for it is found that the headless animal described above will respond in the same manner The placement of the paw is not as accurate and the muscular contractions are not as powerful as the reactions in the normal animal The fact that the paw of the spinal dog is not able to locate the spot on its side that has been stimulated but waves about in the air is an indication of the importance of the higher brain centers in the refinement of reflex movements These centers are also important in producing more powerful contractions than those produced in the spinal animal

Crossed Extension or Mark Time Reflex

If the animal preparation used in the experiment is in good condition and does not show the effects of shock too greatly, the crossed extension or mark time reflex may be associated with the flexor reflex In the former reflex the action of an opposite limb seems to stimulate action in the other That is when the left leg flexes the right leg extends and vice versa As in other reflex movements these are less powerful than the walking movements which they resemble

The flexor and mark time reflexes are excellent illustrations of *reciprocal innervation* (or reciprocal inhibition) Whenever the flexor muscles (those that bend a limb) of the leg contract the extensor muscles (those that extend the limb) relax or vice versa this type of action prevents wasteful effort on the part of one muscle as it tends to pull against the other Evidently, when the flexors receive the impulses from the brain the extensors are relaxed since they are not being stimulated or when the extensors receive the impulses the opposite reaction occurs Contraction of the one set of muscles inhibits the contraction of the other but the inhibition is evidently brought about as stated that is the failure of impulses to excite the one muscle or the other There are no special inhibitory nerves in the central nervous system or no special inhibitory impulses it is merely a matter of fewer impulses coming over the nerves that lead to the inactive muscles

The flexion and extension of the limbs of a spinal animal when the mark time reflex is evident is much more complex In this case it is found that not only does the contraction of the flexor muscle seem to prevent impulses from getting to the extensor muscles of the same limb but also it seems to inhibit contraction of flexor muscles in the opposite limb (the impulse then going to the extensors of this limb) Thus, when one leg is flexed the other is extended

The Knee Jerk or Patellar Reflex

The knee jerk is probably the best known of all spinal reflexes It is a simple reflex that occurs when the patellar tendon is suddenly stretched (the receptors are within the tendon) and causes extension of the leg by contraction of the quadriceps muscle (of the upper part of the leg) Because of the very short reaction time, the response was thought to occur by means of some direct, local effect the stimulus had on the muscle, causing it to contract The reflex disappears, however in the presence of certain diseases affecting the nervous system It is abolished also by cutting either the dorsal or ventral roots of the spinal nerves that innervate the hind limb

In the normal animal, the knee jerk is elicited by means of a single volley of impulses so that the tendency to tetanic contraction in the muscle is hardly noticeable However, it is tetanic, although very short

The knee jerk is absent usually, only when some pathological condition exists It is used clinically along with other tendon reflexes (such as the tendon achilles reflex—ankle jerk) in the detection of certain nervous disorders, such as paresis and *tabes dorsalis* of syphilis poliomyelitis or mechanical injury to the corticospinal tracts of the cord

If other tendon reflexes are present while the knee jerk is absent, it means that the lesion is more or less localized (that is within the reflex arc itself or any part of it), but if other tendon reflexes also are absent then the nervous disorder may be found in the brain itself or it may be due to asphyxia narcosis, etc The reflex is exaggerated if a lesion appears in the pyramidal tracts (Figure 89 page 133) between the brain and the lumbar region of the spinal cord (this condition would be analogous to that of a spinal animal in so far as the patellar reflex is concerned) The knee jerk has probably received more attention than any other reflex because of early recognition of its clinical value. Other reflexes are considered later when the significance of their appearance in certain functions is discussed

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Fulton, J F *Physiology of the Nervous System* 2nd ed (New York Oxford University Press 1943) chs 6 – 8 Reflexes of the spinal cord

10

The Brain and Its Functions

GENERAL STRUCTURE OF THE BRAIN

In the early embryo the nervous system first makes its appearance as a simple tubular structure called the neural tube The brain is derived from this structure Early in development the walls of the tube are very thin but soon cells (*neuroblasts*) are formed that produce neurons and others

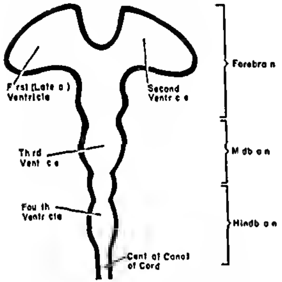


FIGURE 91

Diagram of the embryonic brain and neural tube The forebrain develops into the cerebral hemispheres the neural tube into the spinal cord As the cerebrum develops it folds back and envelopes most of the midbrain and hindbrain

(*spongioblasts*) that produce *neuroglia* which is the supporting tissue of the nervous system At the anterior or head end of the primitive neural tube the brain makes its first appearance in the formation of three dilations

1. Forebrain
   a. Telencephalon
   b. Diencephalon
2. Midbrain
   Mesencephalon
3. Hindbrain
   a. Metencephalon
   b. Myelencephalon (Medulla)

Throughout this development, the hollow tubelike structure is retained and in the region of the original dilations, the cavities form the ventricles of

the brain. Actually this linear arrangement of the final five segments is maintained although it is less obvious owing to the foldings (*flexures*) and irregular thickenings of the walls which enable the structures to fit into the confines of the skull.

MEMBRANES OF THE BRAIN

The cerebral hemispheres, when fully developed, form the largest part of the brain. Surrounding it are three layers of connective tissue which have

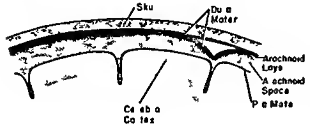


FIGURE 92

The membranes or meninges of the brain in relation to the skull and cerebral cortex.

a protective function. These are the membranes or meninges of the brain and extend backwards to surround the spinal cord which is continuous with the brain.

In direct contact with and following the contours of the brain and cord is the membrane called *pia mater*, containing many blood vessels. The *dura mater*, the outermost membrane, is in contact with the periosteum of the skull. It is made up of strong fibrous connective tissue which forms numerous partitions giving further support and protection to the different parts of the brain.

The *arachnoid layer*, found between the dura and the pia mater, is a rather delicate, transparent membrane and is in direct contact with the dura mater. Between the arachnoid layer and the pia mater is the *subarachnoid space* which has direct communication with the ventricles of the brain and which contains *cerebrospinal fluid*, a colorless lymphlike liquid. The quantity varies between 60 and 200 cc according to the age and size of the individual and is under pressure within the ventricles.

SIZE OF CEREBRUM

In man the largest division of the brain is the *cerebrum* which, if viewed from above, covers all other structures of the brain. The cerebrum contains about ten to twelve billion neurons which is about three fourths of all the nervous tissue in the body. It weighs approximately 1,200–1,500 g, which is at least twice the weight of the cerebrum of the large apes; relatively speaking man has an extremely large cerebrum. It seems certain that the

proportionate size of the human brain is connected with the degree of intelligence reached by man placing him above other animals. However, within the race itself, size is really no index of intelligence; the genius does not necessarily have a larger brain than the idiot, although idiots usually have extremely small brains. The smallest brain ever reported for the human race weighed about 369 g and was that of an idiot, but the largest ever reported weighed 2850 g and was also the brain of an idiot.

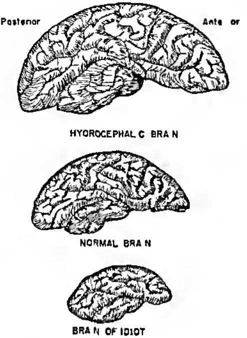


FIGURE 93

Brains of a hydrocephalic idiot (weight 800 grams), a normal human (1200–1500 grams), and an idiot (370 grams).

EXTERNAL STRUCTURE OF CEREBRUM

Very few structures are noticeable on the external surface of the brain. The cerebrum, the largest portion, is divided into two hemispheres by a deep *longitudinal fissure*. Many smaller fissures are seen on the surface but some are not so deeply penetrating as others; these latter are referred to as *convolutions*. In each hemisphere there are other rather deep fissures—the *fissure of Rolando* and the *fissure of Sylvius*—which make excellent landmarks for localization studies. The fissure of Rolando lies slightly anterior to the midregion of the cerebrum. The tissue directly in front of it functions in motor actions at various points in the body, whereas that immediately posterior to the fissure is concerned with sensation.

The convolutions greatly increase the surface of the cerebrum, especially the outermost gray area—the *cerebral cortex*, which in man has an area of about 2 sq ft. The cortex is about 2 to 3 mm thick and is gray in color because of the presence of unmyelinated cell bodies. Microscopically these cells are found in several layers; the large cells are called *pyramidal* cells because of their shape. Usually there are about six layers of cells in the cortex of mammals. Aside from the cortex, the rest of the nervous tissue of the cerebrum is made up of white matter consisting of billions of myelinated nerve fibers, some of which cross back and forth within the cerebrum itself and others which lead down from the cortex to the brain stem and spinal

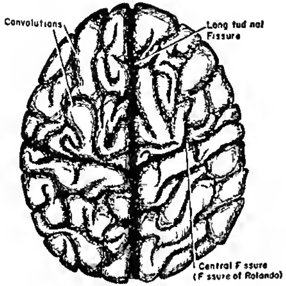


FIGURE 94

Upper surface of cerebrum

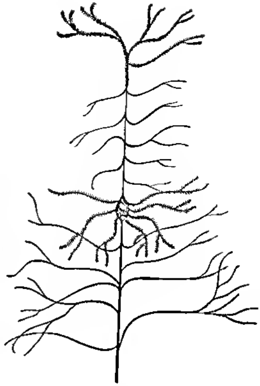


FIGURE 95

Pyramidal cell of cerebral cortex

cord. By means of these fibers any part of the cortex seems to have connection with almost any other part as well as with affectors and effectors in the peripheral parts of the body.

Using the deeper fissures as dividing lines, each cerebral hemisphere can be marked off into four lobes: (1) The *frontal lobe* which takes up the entire region anterior to the fissure of Rolando or central fissure, (2) the *parietal lobe* which lies posterior to this fissure and continues to, (3) the *occipital lobe* which is not separated from the parietal by a deep fissure but rather by a slight indentation of the surface in this posterior region, (4) the *temporal lobe* which lies below the fissure of Sylvius or the lateral fissure.

THE CRANIAL NERVES

If the brain is exposed from below, many more structures come into view (Figure 97), most conspicuous of which are the twelve pairs of cranial nerves. These nerves participate in many reflex actions of the body, some of which are discussed in Chapter 12. Some of them are made up of sensory neurons only (*olfactory, optic, acoustic*), others almost entirely of motor neurons

(*oculomotor, trochlear, abducens, accessory* and *hypoglossal*), and still others have both motor and sensory neurons They are numbered according to their position, the first pair being the most anterior These nerves, their components and their innervations are give in Table 2 (pages 146–47)

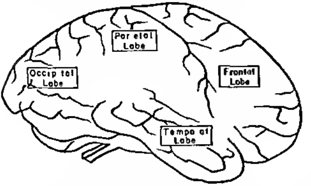


FIGURE 96

Side view of cerebrum showing lobes

Many of the most important reflexes depend on the cranial nerves The impulses that pass over the cranial sensory neurons after stimulation of the receptors enables one to experience sensations of vision, taste, smell, sound

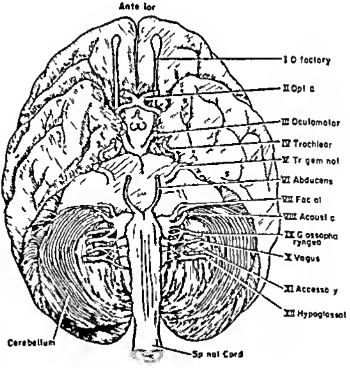


FIGURE 97

View of brain from below to illustrate position of cranial nerves

and touch, of movement, and position in space Some of the impulses from the sensory areas of the brain may continue via motor neurons to glands or muscles which, as a result, are made to secrete or to contract, respectively In fact, excitation of any sensory system may have an effect on almost any part of the body

THE BRAIN STEM

The lowest and most primitive part of the brain stem is the *medulla oblongata* which appears to be merely an expansion of the spinal cord The medulla contains many of the centers that regulate the vital organs Here are found areas that control breathing movements, rate of heartbeat, blood pressure (vasomotor), salivary secretion from parotid glands (these lie immediately in front of the ear and become swollen and painful in mumps), swallowing (movements of tongue and back of throat), masticating (or chewing) reflex, vomiting reflex (activity of stomach, esophagus, muscles of abdominal wall, diaphragm), and coughing, sneezing tear secretion and blink reflexes

The moundlike structures on either side of the ventral mid line of the medulla are referred to as the *pyramids* They contain important motor nerve fibers which originate in the motor area of the cerebral cortex Many fibers cross over at this point (*pyramidal decussation*) and proceed down the spinal cord as the pyramidal tracts eventually innervating skeletal muscles by making synapses with various motor neurons leading to them This explains how the left side of the brain controls the contraction of muscles on the right side and vice versa Sensory fibers may also do this so that loss of sensation on the right side of the body means that the lesion which causes it may be found on the left side of the cerebrum

The bridgelike structure that appears to connect the two cerebral hemispheres is known as the *pons* It carries medullated fibers which lead to the opposite cerebral cortex and cerebellar cortex The pons and the cerebellum are part of the hindbrain (Figure 98)

The *cerebral peduncles* are found in the midbrain and connect the fore brain with the hindbrain They consist of medullated fibers leading from the cerebral hemispheres to the spinal cord

INTERNAL STRUCTURE AND FUNCTION OF THE BRAIN

In Figure 98 a median section shows the internal structure of the brain the *corpus callosum* appearing to be the most conspicuous portion The upper surface of this structure can be seen in an intact cerebrum by spreading the two hemispheres apart at the longitudinal fissure The corpus callosum is very firm compared with the other parts of the brain It consists

TABLE 2

The Cranial Nerves and the Organs Which They Innervate

Number of Nerve	*Name*	*Structure Innervated by Sensory Neurons*	*Structure Innervated by Motor Neurons*	*Effect of Impulse over Nerve*	*Effect of Injury to Nerve*
I	Olfactory	Olfactory epithelium of the nasal cavity	None	Sensation of smell	Loss of sense of smell
II	Optic	Retina of the eye	None	Sensation of vision	Loss of vision
III	Oculomotor	Muscles of the eyeball (muscle sense)	Muscles of eyeball and eyelid Sphincter muscle of iris The ciliary muscles	Movement of the eye and eyelid Constriction of the iris Accommodation of the eye	Drooping of eyelid No constriction of iris Eye fails to accommodate
IV	Trochlear	Muscles of eyeball (muscle sense)	Muscles of eyeball	Movement of eye	Eyeball turns downward and outward
V	Trigeminal	Touch pain and temperature fibers from the face teeth etc	Muscles of chewing Secretory fibers to lacrimal and sweat glands of face	Pain from teeth and face in general Contraction of chewing muscles Secretion of tear fluid and sweat in the face region	Paralysis of chewing muscles (lacrimal and sweat glands) Loss of sensation in face and teeth
VI	Abducens	Muscles of eyeball (muscle sense)	Muscles of eyeball	Movement of eyeball	Possible strabismus (cross eyed)

VII	Facial	Taste buds on front of tongue	Muscles of face and scalp Secretory fibers to salivary glands (sublingual and submaxillary)	Taste for salt, sour and sweet Saliva secretion increased Change of facial expression	Partial loss of taste sense Salivary secretion decreased
VIII	Acoustic	Cochlea Semicircular canals, sacculus and utriculus	None	Sensation of sound Sensation of balance, movement, etc	Loss of hearing Disturbance in balance
IX	Glossopharyngeal	Taste buds on back of tongue Walls of pharynx	Muscles of throat Secretory fibers to parotid (salivary) gland	Taste is bitter Swallowing reflex Secretion of saliva	Partial loss of taste Failure to swallow Decreased salivary secretion
X	Vagus	Lungs Larynx Arch of the aorta Stomach	Heart Stomach Small intestine Larynx Esophagus Gastric glands	Lung reflex Depressor effect in aortic bodies Sensation of hunger Inhibition of the heartbeat Acceleration of stomach and intestine action Swallowing (esophagus)	Difficult breathing Difficult swallowing Slowing of respiration Increase heartbeat Decrease movements in alimentary tract (except sphincters)
XI	Accessory	Muscle sense in muscles of upper trunk	Muscles of upper trunk region	Contraction of shoulder muscles	Paralysis of muscles in shoulder girdle (those concerned with turning the head)
XII	Hypoglossal	Muscle sense in tongue muscles	Muscles in tongue	Movements of tongue	Difficulty in speech and swallowing

of bands of fibers, connecting one cerebral hemisphere with the other, which evidently function in coordinating the two halves The *third ventricle,* from which lead the two lateral ventricles (not visible in median section) via the *foramina of Monroe* lies just below the corpus callosum and leads into the *fourth ventricle* posteriorly, via the *cerebral aqueduct* The latter is a

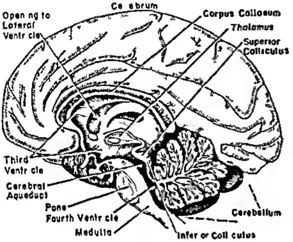


FIGURE 98

Median section of brain showing relationships of various structures

rather narrow tubelike structure above which are two pairs of very important bodies, the *superior and inferior colliculi,* which as a group are referred to as the *corpora quadrigemina* Pathways from the retina of the eye lead into the superior colliculi where they make synapses with motor neurons leading out by way of cranial or spinal nerves In the same way auditory fibers lead into the inferior colliculi where they also pass their impulses on to motor fibers

The *thalamus* is another organ of importance as a ' receiving station It is intimately connected with the striate body (*corpus striatum*) which consists of two distinct masses of nerve cells, the *caudate nucleus* and the *lenticular nucleus* (a nucleus, in this sense, is similar to a ganglion except that it is contained within the brain whereas a ganglion is external to the brain or cord) There is also a richness of connections, in both ingoing and outgoing fibers between the thalamus and the cerebral cortex These consist of optic, auditory, cutaneous and other sensory tracts The thalamus and striate body together have been regarded by some as a subsidiary cerebral cortex There are many nuclei within the thalamic region, some of them appear to play important roles in complex muscular movements

THE THALAMO STRIATE BODY

In lower mammals, the entire cerebral cortex may be removed and the animal will continue to live normally in many respects, but all coordination

seems to be lost if the "thalamostriate brain" (the thalamus and striate body) is removed. In humans along with other functions it evidently controls emotional movements concerned with laughing and crying. Injury to this body results also in an inability to stand erect when the eyes are closed, a symptom characteristic of *tabes dorsalis*, a degenerative condition associated with syphilis.

It is believed that in humans the thalamostriate body may often carry on functions that were formerly centered in the cerebral cortex; that is, injury of a particular part of the motor cortex may not necessarily cause paralysis of the muscles controlled by that part since the thalamostriate body evidently takes over the control.

THE HYPOTHALAMUS

The hypothalamus lies below the third ventricle and contains several physiological centers. Afferent fibers reach it from the cerebral cortex, thalamus, and brain stem, and efferent fibers lead from it to the thalamus, brain stem, cord and pituitary gland. In its anterior portion are found several centers: (1) the *parasympathetic center*, so-called because upon stimulation of this area several activities associated with parasympathetic stimulation are produced, such as slowing of the heart, hyperinsulinemia (high concentration of insulin in blood), and urination, (2) the *carbohydrate regulating center*, (3) the *sleep center*, (4) the *hunger center*, (5) *a heat regulating center* (decreases temperature) in that stimulation results in sweating and hence the dissipation of heat, and (6) a center located in the hypothalamus which regulates the production of the antidiuretic hormone of the posterior pituitary. A lesion in this particular area may result in a great increase in urine flow (a symptom of *diabetes insipidus*).

In the posterior part of the hypothalamus are found several centers antagonistic to those of the anterior, namely, (1) the *sympathetic center*, (2) the cardio accelerator center, (3) the vasoconstrictor center, (4) the heat regulating center (increases temperature), and (5) a fat metabolism center. The noticeable autonomic effects brought about by thought (emotional) may be owing then to the effects of impulses produced in the cerebral cortex upon the hypothalamus.

up of medullated fibers for the most part On the other hand, the cerebrum and other areas of the brain contain many "centers" (some of these have been mapped out especially for the cortical regions) which exercise the power of control over all parts of the body These centers are made up of 'gray" matter and consist of unmedullated parts such as cell bodies, and dendrites of the nerve cells Obviously, then, the so called "white" matter functions in the conduction of impulses whereas the "gray" matter functions in control and integration

CEREBRAL FUNCTION IN VARIOUS VERTEBRATE TYPES

It has been pointed out previously that ascending from the lowest to the highest vertebrates, the development of the cerebrum becomes more and more marked, compared with other structures in the brains of animals, such as olfactory lobes, optic lobes, and so forth In Figure 99, the brain of a

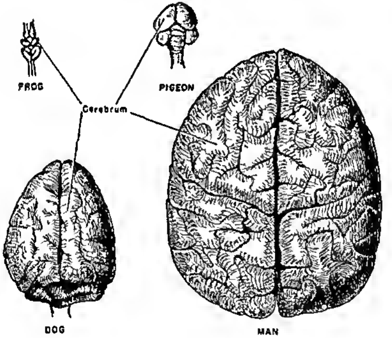


FIGURE 99

A comparison of the brains of various vertebrates

fish, frog, reptile, bird and man are shown and illustrate these differences It is the possession of a well developed cerebrum (cerebral cortex) that enables the human race to excel all other animals in intelligence The fact that the lower vertebrates do not depend very much on the cerebrum can be

demonstrated by removing this part of the brain and observing the general behavior of the animal.

If the cerebrum of a fish is removed, there is very little change in the animal's reactions. It shows the same ability to move and swim about as a normal animal. It can discriminate between food material and undesirable objects. Such a fish may tend to be somewhat inactive compared to others but it will mingle with them and cannot be distinguished from them. The removal of the cerebrum of the frog also shows very little effect on its behavior if care is taken not to injure the midbrain. It can jump, swim, and maintain a normal posture. It will avoid obstacles that have been placed in its way. Most of these reactions are shown, however, only when the animal is stimulated. Otherwise it tends to be inactive, evidently because it does not benefit from past experiences without its cerebrum. In a frog with an intact forebrain or cerebrum, the croaking reflex is definitely under voluntary control. In the absence of the cerebrum, however, there appears to be very little inhibition, and the frog will croak if its back or sides are stroked.

The effects of removal of the cerebrum in birds are much more obvious than in the case of the lower forms just discussed. Immediately following the operation and for some time after, the bird is very inactive. It remains at rest, standing on one leg with its bill buried in its breast. Occasionally it will stretch itself or walk about. Of course, if the bird is forced into other activity it will respond automatically. Thus, if it is thrown into the air it will fly or if placed on its back it will right itself, but it does not make spontaneous movements, except for those mentioned above.

In the lower brain centers of the bird there appears, in time, to be a gradual development of other activities that had evidently been suppressed, for eventually, the bird apparently overcomes its inactive condition and will move about constantly. It responds to many types of stimuli but will not eat unless food is placed in its mouth. There is a complete loss of sex interest as well, and a female will no longer care for its young.

The removal of the cerebrum in mammals is more difficult to perform than the removal of that in birds, as might be expected. Investigations have been carried out chiefly on dogs and cats. Such animals may live for several years. They do not move about for many hours (or even several days) after the operation but soon periods of activity and inactivity reappear and the animals may move from one place to another spontaneously. Dogs treated as described react to stimulation by snarling or barking and the ears may take on an erect position, but they do not display any signs of recognition.

Although removing the cerebrum of these various types of animals indicates that the effects become greater and more complex in higher mammals it can be concluded in a general way that all of these animals display the same general defects—a loss of memory and intelligence which results in a loss of normal behavior

LOCALIZING REFLEX LEVELS OF THE CENTRAL NERVOUS SYSTEM

There are now standard procedures for demonstrating functions at various reflex levels of the central nervous system These consist of operations which involve sectioning the brain and cord enabling investigators to localize

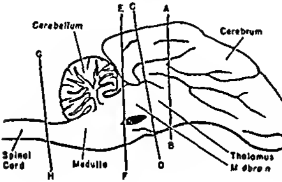


FIGURE 100

Brain of a cat indicating the cuts necessary to produce a spinal animal (G–H), a decerebrate animal (E–F), a midbrain animal (C–D) and a thalamic animal (A–B) (After Bond)

numerous functions The various cuts are illustrated in Figure 100 and consist of (1) A cut through the approximate point of union of the brain (medulla) and spinal cord, such a section results in a *spinal* animal (2) A cut made between the medulla and midbrain, which contains the thalamus and many surrounding nuclei, all of which would be removed in the operation an animal so treated is called a *decerebrate animal* (3) A cut made through the midbrain between the thalamus and red nucleus (a rather vascular area just posterior to the thalamus), resulting in a *midbrain* animal (4) A cut made above the thalamus, producing a *thalamic* animal

The Spinal Animal

The spinal animal has been studied to some extent in a previous chapter It will live for several hours to several days with many of its mechanisms functioning normally, provided that artificial respiration and warmth are applied to it It shows no outward signs of activity and remains motionless unless stimulated

The animal is unable to breathe and will be limply since there is a complete loss of muscular tone Its blood pressure which decreases very markedly immediately following the operation begins to rise again soon

afterwards although it remains much less than it was normally, this indicates the presence of a vasomotor control center within the spinal cord

The Decerebrate Animal

If the cut is made just in front of the medulla as described above, a decerebrate preparation is obtained One of the outstanding characteristics is the appearance of an extreme tonus in the muscles of the preparation The limbs become stiff and the condition is referred to as *decerebrate rigidity*" Since the medulla is intact, all the reflexes that were mentioned in a previous discussion of this structure are present in this animal It can breathe spontaneously and the activities of the other vital organs appear to be normal However, except for these reflexes, the animal does not move unless stimulated, and it is unable to maintain its temperature at a proper level The important heat regulating center, as already pointed out, is placed at a still higher level in the brain

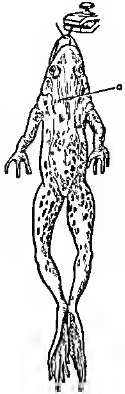


FIGURE 101

Spinal frog illustrating limpness due to loss of muscular tone a incision at which cord was severed

The absence of inhibitory influences from higher brain levels is also characteristic of the decerebrate preparation The respiratory movements are overactive, and a supertonus exists in the muscles because of the fact that control has been at least partly lost

A drawing of a decerebrate cat is shown in Figure 102

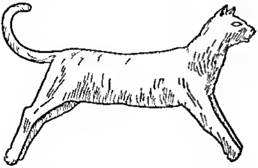


FIGURE 102

Sketch of a suspended decerebrate cat showing decerebrate rigidity

The Midbrain Animal

In the midbrain animal it will be recalled, the red nucleus and others near it are left intact It was at one time thought that the red nucleus was in

volved in proper muscular tone, because, when it is present, the animal does not show signs of rigidity However, it has been shown recently that the red nucleus can be removed separately from this part of the brain without the appearance of the rigid condition There are many other centers in the region of the red nucleus which might play a role in normal muscular tone It is now believed that a reticular area in the bulbar portion is responsible for inhibition of this supertonus The midbrain animal stands in an almost normal manner, as contrasted to the decerebrate animal which cannot do so, and can right itself if placed on its back This 'righting reflex' is not shown by the decerebrate or spinal animal Normal posture and standing in man depend upon other more complex factors such as the eye and its movements as well as the labyrinths of the inner ear

The Thalamic Animal

The thalamic animal, in which the section passes above the thalamus, possesses much more complex behavior patterns The neck and labyrinthine or inner ear reflexes, which function in balance and normal posture, are evident and muscle tonus is normal Spontaneous and coordinated movements are carried out by this animal such as stepping, walking, and the like, although usually it sits still and only occasionally gets up and walks The movements it does carry out, however, are very effectively executed

Temperature regulation is evidently controlled within the thalamic region, for the animal is capable of maintaining normal temperature In lower mammals the thalamus is the chief sensory center and is far more important to them in this capacity than to man It is sometimes referred to as the *optic thalamus* in these animals because of its relation to vision Much more complex relationships exist in man

Evidently the ability to feel pain is centered in the thalamus (as is also the appreciation of extreme temperatures) for if it is destroyed the power to feel pain is lost This is not true if the cerebral cortex is destroyed, in which case, pain is felt but no distinction may be made between kinds and extremes of pain Thus, the cortex adds to the power of distinguishing between types and intensities of pain

THE CEREBRAL CORTEX

The cerebrum has been regarded as the seat of consciousness since the time of Hippocrates (460–377 B C) It was believed then that the power of imagination was centered in the frontal lobes, intelligence in the central portion, and memory in the occipital lobes of the cerebrum This centralization of consciousness in several definite lobes or areas finally led into the

pseudo science of phrenology, or the assumption that ability could be predicted by noting the relative sizes of parts of the head These functions are now thought to be performed by certain rather vague areas of the cortex of the cerebrum, called the association areas

No longer are separate parts of the cerebral cortex looked upon as having to do with "mind" but the behavior of the organism as a whole is considered as an expression of the presence of mind The frontal lobes, for example, are no longer thought to be the seat of intelligence True enough, the idiot often has extremely small frontal lobes, but in normal man, considerable areas of the frontal cortex have been injured without loss of intelligence

The study of the functions of the cerebral cortex has been approached from several directions (1) In gross and microscopic anatomy are found differences in normal and abnormal conditions of the cortex (2) In embryology, a study of the development of the cortex of individual animals may be made and compared with their behavior (3) Comparative anatomy aids greatly in understanding various types and stages of cerebral development as found in the different animals studied (4) By means of physiological methods much can be learned about location of centers in the cerebral cortex This may be done by exposing the surface of the brain and stimulating the cortex This was first attempted by Fritsch and Hitzig in 1870, who stimulated the cortex of dogs with galvanic current Another method is to remove or destroy parts of the cortex and note the changes in behavior brought about by the removal In humans, clinical observations may be made on individuals who have suffered brain injuries or have been afflicted with lesions due to nervous disease

All of the above methods have aided in localizing and understanding the functions of the various parts of the cortex

THE MOTOR CORTEX AND MOTOR POINTS

That part of the cortex which is situated at the posterior portion of the frontal lobes is referred to as the *motor cortex,* since it has been shown that stimulation of this area, just anterior to the fissure of Rolando (central fissure), on one side of the cortex causes movement on the opposite side of the body

Within the motor cortex are found large *pyramidal cells* (Figure 95) They definitely function in motor activity, since any lesion in the pyramidal tract, which leads from the cortex to levels of the spinal cord, produces paralysis of voluntary movement, tonus is still evident, however, because afferent fibers still have access to efferent fibers leading to muscles from the spinal cord

In mapping out the motor areas of man it is found that the motor points are arranged in a definite pattern, and in complete reversal to the regions of the body which are controlled by those areas It has been mentioned previously (page 145) that voluntary movements of the right side of the body are initiated by activities of the left cerebral hemisphere In addition, if the cortex is stimulated with fine electrodes, from the medial surface of the cortex laterally, movements of the lower limbs will be observed first, then of the trunk, upper limbs and face, in that order Using this procedure, many motor points have been mapped out in the cortex (Figure 103)

The movements are remarkably similar to the movements produced voluntarily However, the reaction that is produced when a particular point is stimulated is not always predictable Different movements may be obtained by stimulating the same motor area under different conditions For example, the degrees of narcosis, temperature and the like, varying from one stimulation period to the next, may bring about a change in response

Much of the work on localization in motor areas has been done on the chimpanzee It has been shown that localization in man is very similar to that of this animal and other anthropoid apes These animals have been used especially in work concerned with the removal of part of the cerebral cortex which is another means for demonstrating localization

For example, if an area such as that designating an arm area in Figure 103

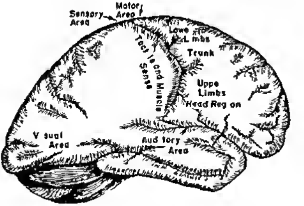


FIGURE 103

Surface view of cerebrum indicating locations of motor and sensory areas

is removed there is immediate loss of movement in the arm of the opposite side (sensations in this arm, however, still persist) Gradually, over a period of five to seven weeks there is a recovery of this lost power until the responses of the arm are almost normal again There is only a slight awkwardness and clumsiness of movement which distinguishes between the two arms Similar observations have been made on humans whose motor areas have been injured Here, also, there is a gradual recovery but the awkwardness is much more noticeable in man than in the apes

It is not known how this phenomenon is accomplished, that is, how this gradual recovery takes place There is no regeneration of the lost cortical region Perhaps some other part of the cortex takes over the function of the lost part, although evidence cannot be produced for this supposition, since there is no area on the motor surface of the cortex which when stimulated electrically, brings about a response in the affected arm

THE SENSORY CORTEX

The sensory areas of the cortex which lie within the parietal lobe behind the fissure of Rolando are not so well defined as the motor areas The area lying immediately behind the Rolandic fissure, and parallel with the motor cortex, is evidently the seat of cutaneous as well as deep sensations An animal cannot express his sensations and for this reason it is obviously much more difficult to localize areas in the sensory regions of the cerebral cortex than in the motor, where muscular contraction is depended upon as an expression of conduction from a particular area Since such animals as the dog do respond to pain, centers for this type of sensation may be found more readily than for other types

THE LOBES OF THE BRAIN

The *frontal lobe* has often been termed the seat of intelligence This conception probably dates back to the time of the phrenologist Gall (1810) and later it became fashionable to ascribe each specific function to a specific area in the brain It had been noted that idiots usually show atrophy of the frontal area of the cerebrum and also that lesions and tumors produced in this area often affect the intelligence of the individual Many now believe however that intelligent behavior is a function widely distributed throughout the cerebral hemispheres and some even take the view that intelligence is expressed only in the form of the behavior of the organism as a whole It is true that the thickness of the outer cell layer (cortex) of the frontal lobes seems to vary directly with the mental capacity of the individual This is also true of the cortex of the *parietal lobe* These two lobes aside from their functions already described are also great association areas and in this respect have considerable to do with the intelligent behavior of animals

The cortex of the *occipital lobe* functions in vision Fibers from the thalamus transfer the impulses coming to it from the retina via the sensory tracts after decussation or crossing over of some of the impulses at the *optic chiasma* (the area at which the optic nerves cross over) The right occipital lobe receives impulses from the right side of each retina the left occipital lobe, from the left side of each

A large part of the cortex of the *temporal lobes* is concerned with hearing The structure of this region is quite similar to that of the visual area of the occipital lobe The nerves leading from the auditory end organs in the cochlea terminate in the temporal lobe The receptors of the vestibule (the entrance to the inner ear), which are concerned with equilibrium, also send fibers to this region

INJURY TO THE CEREBRUM

As has already been pointed out, injury, removal or disease of a part of the cerebrum, may have an effect which varies with the location and extent of injury, that is, injury to a small part of the motor or sensory area will result in paralysis or loss of sensation, respectively, in some region on the opposite side of the body Injury to the visual area of the occipital lobe may result in blindness, to the temporal lobe, deafness, and to the anterior end of the temporal lobe, loss of the olfactory sense

Aphasia or loss of power to speak may result if the speech centers of the frontal and temporal lobes are injured Aphasia may exist as either a motor or sensory malfunction In the former type, the individual is unable to speak but this is not caused by paralysis of the muscles concerned in articulation On the contrary, owing to lesions in the cortical areas involved the person cannot utilize the association areas for producing integrated and coordinated movements of the muscles

The sensory type of aphasia may be owing to word blindness, the inability to understand or comprehend written words, or to word deafness the inability to comprehend spoken words

THE CEREBELLUM

The location of the cerebellum or little brain' and its close association with other brain structures has already been described

Fissures cover the surface of the cerebellum and are of a much finer texture than those of the cerebrum The gross internal structure of the cerebellum is treelike, it consists of two hemispheres which are joined by means of

FIGURE 104
Sagittal section through the cerebellum showing treelike structure produced by fissures

a central portion—the *vermis* The cerebellum reaches its greatest development in apes and man In reptiles and amphibians it is a rudimentary organ and its removal has no noticeable effect on the behavior of the organism In mammals, many functions have been assigned to it by various investigators especially in the past It is now known to function in the coordination of muscular movements, both those concerned with voluntary acts and those concerned with posture

The cerebellum receives impulses from all parts of the nervous system Because of its intricate structure it presents reflex arcs of great complexity Afferent fibers come to it by way of the spinal cord and medulla Efferent pathways appear to have their beginnings in the peculiar *Purkinje cells* of the cerebellar cortex The Purkinje cell with its many ramifying dendrites is shown at A in Figure 105 The axons from these cells pass down through the medullary layer, they are efferent neurons and all other neurons within the cerebellum are thought to be afferent

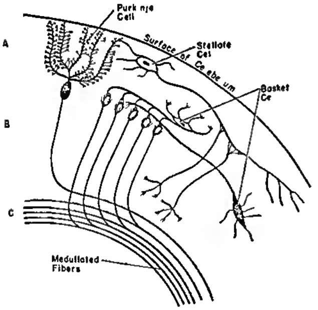


FIGURE 105

Diagram of a transverse section through a small area of the cerebellum A external molecular layer B middle granular layer C internal layer consisting of medullated fibers

From the clinical observations made on various types of lesions, wounds tumors or other injuries of the cerebellum it has been found that the organ has nothing to do with sensation and that the abnormal behavior resulting from its injury may be due to loss of tone in the skeletal muscles

An animal from which both the cerebellum and cerebral cortex have been removed (that is, a thalamic animal minus the cerebellum) does not show any considerable change in behavior It can behave in a manner quite similar to that of a normal animal Thus since in-coordination is not associated

with the removal of the cerebellum in a decorticate animal it appears as though the cerebellum exerts its influence chiefly on voluntary movement However, even though it transmits the impulses which are produced in the cerebral cortex, none of its activities enter into consciousness

Lesions in certain areas of the cerebellum may bring about an unsteady swaying and weakened type of movement That is the muscles on the same side of the body as the injury may lose their tone (*atony or hypotony*) Their contractions may be weak (*asthenia*) and unsteady (*astasia*) and there may be loss of purposeful action of the muscles (*ataxia*)

Partial removal of the cerebellum produces a much greater effect than complete removal because of the resulting imbalance of the former Thus a dog may have much greater difficulty getting to a bowl of food when only one half the cerebellum is removed than when both sides are removed

In summarizing it appears that the cerebellum functions in (1) coordination of voluntary movements and (2) tonic conditions of skeletal muscles concerned with equilibrium

ADDITIONAL READING

Krieg W J S *Functional Neuroanatomy* 2nd ed (Blakiston 1953) ch 16 Cerebral cortex

on a light placed near the eye and rings a bell, the pupils of his eyes will contract because of the light effect. If, at the word "relax," the subject releases his grip, the light goes out, and the bell stops ringing, the pupils expand. After numerous repetitions, it has been found that ringing the bell or merely saying "contract" with no light or bell causes the pupils of some individuals to contract and the word "relax" causes them to expand.

There are many examples of conditioned reflexes serving man in a purposeful way. As a matter of fact, nearly all mammalian behavior is based upon conditioned responses such as learning to perform a skillful manipulation, as the athlete learns to respond immediately to certain conditions, or as the child learns to carry out everyday activity by repeated performance. The rate of learning depends upon the rate at which conditioned reflexes may be developed.

THE PHYSIOLOGY OF SLEEP

Most animals have periods of rest and periods of activity which are more or less rhythmically regulated. Sleep in higher animals compares favorably with the rest period of lower forms. The common earthworm is said to exhibit four periods of rest during each twenty four hours. If it is cut in two, each half continues to exhibit these four periods, indicating that the brain or anterior ganglion centers are unnecessary. In mammals, however, it is found that when a cut is made between the spinal cord and brain, the posterior part of the body shows nothing that might be interpreted as periodic sleep, whereas the anterior part continues to go through periods of rest and activity. These observations indicate that although rest does not appear to be the function of higher nervous centers in lower animals, it is associated with brain function of mammals and birds.

In order to overcome the effects of fatigue and exhaustion, it is apparent that activity must sooner or later be followed by rest. It is said that the human adult requires seven to eight hours sleep every twenty four hours. This figure naturally meets with considerable variation. Generally speaking, however, children require much more sleep than adults; their activity is great and their stored energy relatively small compared with that of the adult. Their periods of recuperation are, therefore, much longer. In old age, on the other hand, lowered metabolic rate and decreased activity are found; therefore, the need for sleep lessens.

The desire to sleep is manifested by "heaviness" of the eyelids, dryness of the eyes, and difficulty in fixing attention. Normally this state sooner or later gives way to unconsciousness, at which time the cerebral cortex is not visibly affected by external or internal stimuli. The excitability of many

reflexes is diminished during sleep Some, such as the knee jerk (patellar reflex), disappear completely as a result of the loss of muscle tone

CHARACTERISTICS OF SLEEP

The onset of sleep is favored by relaxation, quiet, and darkness These conditions naturally protect the sense organs from external stimuli, and thus the cortex is not called upon to work The eyelids are drawn together and the eyeballs are rolled upward and inward The pupils of the eye are constricted during sleep, this is one way of differentiating between true and feigned sleep

Sleep is characterized by changes in the usual activity of many organs Respiration usually becomes slower and more regular These respiratory movements are often accompanied by noises (snoring) produced by the air passing over and causing vibrations of the uvula and the folds of the larynx which are readily affected because of their almost completely relaxed condition During the onset of sleep, respiratory movements may be irregular and jerky due to irregularity of the speed at which loss of consciousness occurs

During sleep the frequency of the heartbeat is greatly reduced and the blood pressure lowered, except during periods of dreaming when both may increase to a point above normal The volume of various parts of the body especially the limbs, increases during sleep which suggests that the blood vessels in these structures become dilated The basal metabolic rate is reduced considerably (by almost 10 per cent) There is also a slightly lowered body temperature and decrease in muscular activity (tonic and tetanic) Dreaming may cause considerable variation in basal metabolism and is one reason why the basal metabolic rate is not measured during sleep Another reason is that in spite of lowered tonus, movements occur frequently in changing position during sleep (about every 10 to 30 min), this would make the metabolic rate very irregular

DEPTH OF SLEEP

Depth of sleep is very irregular It can be determined by finding the intensity of a stimulus, usually of sound, necessary to awaken the subject Naturally, there is considerable variation in different subjects but in general the results, which can be expressed in the form of a graph, show that depth of sleep increases steadily and reaches its maximum somewhere between one to two hours after its beginning It then decreases to a point where sleep is very shallow for two or three hours but the depth may increase slightly

again at the fifth or sixth hour after which it decreases and remains shallow until the subject awakens

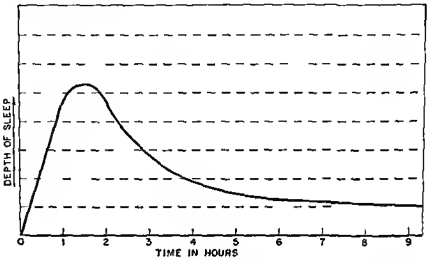


FIGURE 106

Graph showing approximately the depth of sleep at various periods after its onset *In the average individual greatest depth evidently occurs between one and two hours after onset*

FATIGUE AND SLEEP

Kleitman whose book *Sleep and Wakefulness* is outstanding in this field has emphasized the role played by relaxation in sleep Sleep can be induced even in the absence of fatigue when a person or animal is made to relax Relaxation is associated with a decrease in nerve impulses from the cerebral cortex to the musculature of the body at the same time that there is a decrease in the number of afferent impulses that reach the cortex

When fatigue increases sleep occurs more readily This fact has been the basis of the proposed chemical theories of sleep Such theories assume that fatigue appears because of the collection of waste products, lactic acid and other intermediate products in the blood and ultimately in the brain centers concerned with sleep It should be noted however that sleep occurs in the absence of fatigue and therefore the latter may be only another factor which is favorable for the onset of sleep

THEORIES OF SLEEP

Many theories and explanations for sleep have been advanced but as yet none are wholly satisfactory A few of the more important are here presented

1 *The Mosso Howell cerebral anemia theory* was the outcome of observations made upon circulatory changes during sleep. Many investigators had noticed that during sleep there is an increase in volume of the extremities of the body. Since such a change might denote the increase in diameter of the blood vessels, it was suggested that, because of this increase, blood was shunted away from the brain, causing a condition similar to that found in fainting, that is, a low blood or hemoglobin content in the brain, an anemic condition. But the evidence is against the occurrence of cerebral anemia during sleep and it has been found that, on the whole, the circulatory changes present during sleep are the result of rest during sleep rather than the cause of sleep.

2 The theory that sleep occurs because of the *inhibition of conditioned reflexes* was advanced by Pavlov as a result of his studies of the process of conditioning dogs. He maintained that when a conditioned response was being extinguished or inhibited by constantly applying the conditioned stimulus without the unconditioned, the animals on which he worked became drowsy and fell asleep. As is true of all sleep theories, this one has been incompletely studied and, therefore, not wholly acceptable.

3 The *chemical theory*, which has already been mentioned and which has perhaps been the most acceptable in the past, is not at present held in such high esteem. Surely, high concentrations of products of metabolism favor sleep, but until further evidence is available, these products must be considered only as factors which enhance the onset of sleep. In recent years, observations have not supported this theory. There were born in Russia in 1938, twins with bodies joined to form one, but with heads and arms separated. They lived somewhat less than two years. Each had a separate nervous system but their circulatory systems were united. Thus the same blood ran through the vessels of both. It was found that after periods of activity one of the heads would sleep while the other could remain quite active (Figure 107). This, of course, immediately suggested that a chemical theory for sleep was out of the question. The same chemicals were carried to both brains, yet they did not react the same. However, this theory cannot be dropped without further work for it is quite possible that the nerve cells of the brain centers of the one, because of greater use, had become more susceptible to chemical actions than those of the other.

4 Kleitman's suggestion that sleep is a result of loss of muscular tone through fatigue of some neuro muscular mechanism, is looked upon with favor (in other words a relaxation is produced). Certainly, sleep is avoided by muscular activity whereas inactivity or relaxation is conducive to sleep even in the absence of fatigue.

FIGURE 107

Coalescent twins with separate nervous systems but with circulatory systems merged so that both use the same blood they may sleep at different times. At left Galya cries while Ira sleeps below. Ira smiles and lifts her head when her name is called but Galya lies unresponsive and composed. (By permission of Sovfoto.)

CEREBRAL MECHANISMS INVOLVED IN SLEEP

There has been considerable controversy as to what part, if any, that the cerebral cortex plays in sleep. It is certainly not the all important center for it has been found that decorticate dogs, cats and other animals show periods of sleep and wakefulness. This fact places emphasis upon some subcortical area as a center of greater importance for sleep than the cortical. A clue to the importance of some subcortical region in this connection was supplied by observations made upon patients suffering from a form of sleep-

ing sickness, *lethargic encephalitis* (an epidemic had spread through southern Europe during the years 1889 and 1890) The sleep produced by this disease is closely allied to normal sleep in that the patient can be aroused, at least momentarily Upon autopsy of fatal cases it was found that lesions had occurred in the region of the hypothalamus More recently it has been experimentally shown that sleep can be produced in animals by stimulating the hypothalamic region of the brain Electrodes were placed in the brain stem (hypothalamus) of cats or dogs After the wounds healed, it was found that when a stimulus of low intensity was applied, the animal fell into a state of sleep which in every respect was similar to normal sleep

On the other hand, removal of areas of the hypothalamus may cause a condition of continued sleep Thus it appears that two centers may be concerned, sleeping and waking, the latter is responsible for the maintenance of excitability of neurons in the hypothalamus, but may be depressed if the sleep center, in the suprachiasmic area (above the region where the optic nerves cross), becomes increasingly active When this occurs, then, sleep follows However, the importance of the cerebral cortex cannot be disregarded, and it is claimed that anesthetics may produce their effects by action on the cortical cells, thus producing sleep Other drugs such as caffeine may act by increasing cortical activity, thus tending to inhibit sleep

ADDITIONAL READING

Kleitman, *Sleep and Wakefulness* (University of Chicago Press, 1939)
Nauta, W J H "Hypothalamic Regulation of Sleep in Rats An Experimental Study," *Jour Neurophysiol*, 9 285, 1946

12

The Autonomic Nervous System

All vertebrates have central nervous systems, they also have autonomic (*visceral*) nervous systems which are involuntary in action and innervate smooth muscles, cardiac muscles, and glands The name, autonomic nervous system, was first suggested by Langley in 1898 It is commonly known that breathing movements, heart action, secretion and movements of intestines, and similar body activities are all involuntarily controlled, this is owing to the fact that they are innervated by autonomic nerves Although, there is a lack of voluntary control, the central nervous system is indirectly involved in autonomic activity There are many reflexes concerned with internal adjustments (heart action, blood pressure, and the like) of which one is never conscious The stimuli that evoke the responses occur within the body For example, stretch receptors in the carotid sinuses (which are pouches in the carotid artery leading to the brain) are stimulated when the blood pressure increases Impulses are transmitted over afferent autonomic nerves to centers in the medulla which are, in turn, stimulated to initiate impulses over special efferent nerves that cause the smaller blood vessels to dilate (smooth muscles in walls relax) and cause a fall in blood pressure Actually the autonomic neurons (fibers) arise from the central nervous system (C N S) Afferent neurons of the autonomic nervous system (A N S) follow the same pathway as the afferent (sensory) neurons of the C N S into the cord or brain However the autonomic neurons which carry the impulses from the cord or brain, make synaptic connections in "peripheral Ganglia" and form plexuses which are never found in the C N S

Originally, the autonomic nervous system was thought to consist only of a chain of ganglia on each side of the vertebral column, beginning with the cervical ganglia in the neck and ending with those in the sacral region Fibers lead from these ganglia to various visceral organs hence the term sometimes used—*visceral nervous system* It is now known that the A N S consists of two subdivisions, the parts of which differ in structure and function (1) the *sympathetic* (or thoracolumbar) division consisting of a row of ganglia on either side of the vertebral column between the upper thoracic region and the lower part of the lumbar region and (2) the *parasympathetic*

(or craniosacral) division originating from the medulla and midbrain (cranial) and the sacral part of the cord

The fact that autonomic neurons innervate only smooth muscles and glands, and never skeletal muscles, is significant The action of smooth muscles and glands is quite different from that of skeletal muscles in that the smooth muscles may be in a state of partial contraction or glands may secrete small quantities of fluid most of the time At any moment the contraction of smooth muscle or secretion of glands may become greater or less if necessary

For the most part, each muscle or gland innervated by the autonomic system receives neuron fibers from each division, that is, the visceral organs are doubly innervated For example, if the nerves of the sympathetic division leading to the heart are stimulated, the heart beats more rapidly, whereas stimulation of the parasympathetic nerves leading to the heart will decrease or stop its activity On the contrary, if the nerves of the sympathetic division leading to the intestine are stimulated, there is a retardation of its action, whereas stimulation of the parasympathetic nerves increases intestinal activity Whether or not a muscle will contract or a gland will secrete more or less depends upon the intensity of the stimulus applied to one set of fibers as compared with the other

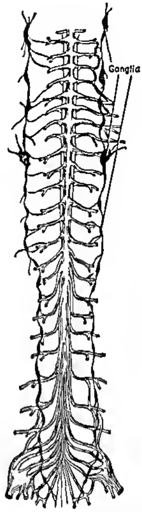


FIGURE 108

The nerves and ganglia of the sympathetic division of the autonomic system in relation to the central nervous system

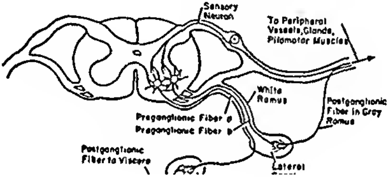
Autonomic fibers are, by definition, often looked upon as efferent only From more recent knowledge of the true structure, gross and microscopic, of this system it has been definitely established that sensory, or afferent, fibers also are present and that many reflexes are evident (Bainbridge reflex, Hering Breuer, or lung reflexes, carotid sinus reflex, and others)

THE SYMPATHETIC (THORACOLUMBAR) DIVISION

The most obvious portion of the sympathetic division consists of twenty one or twenty two pairs of ganglia lying in a lateral chain, so called because

they lie near to or laterally to the vertebral column. These ganglia represent points of synapse between neurons forming pathways to structures to be innervated and, for the most part, are composed of nerve-cell bodies Although these ganglionic chains extend from the cervical to the sacral regions, actually the nerve pathways which lead to or through them originate in the thoracic and upper lumbar regions of the spinal cord. Thus, the name "thoracolumbar" is used to describe this division.

Upon observation it appears as though each ganglion is connected with the spinal cord by means of a spinal nerve. However, as can be seen in Figure 109, the ganglia are connected by way of their own neurons which lead



characterized by the absence of the myelin sheath and for this reason are mostly grayish in color. Those preganglionic fibers that end in the ganglia, make synapse with postganglionic fibers that return to the spinal nerve by way of the *gray ramus communicans*. Thus, the spinal nerves are actually mixed, central and autonomic neurons, but the large number of medullated fibers overshadow the gray autonomic fibers so that the white color of the nerve predominates. These sympathetic fibers that follow the nerve trunks carry impulses to the blood vessels of skin and skeletal muscles, to the smooth muscles of the hairs, and to sweat glands. All the preganglionic fibers of the sympathetic division do not make synapse with postganglionic fibers in these ganglia. A few myelinated fibers (giving the light appearance of the white ramus) pass on through the lateral ganglia, form the splanchnic nerves (inhibits movement of stomach and intestine), and end in the *collateral plexuses*. These plexuses lie further from the vertebral column and nearer to the viscera, such as the *coeliac plexus* or *solar plexus, superior mesenteric plexus* and *inferior mesenteric plexus*. In these ganglia, the preganglionic fibers make synapse with postganglionic fibers which lead to the alimentary canal and closely related structures.

The pathways followed by the neurons are the same on either side of the cord but in Figure 109 only the sympathetic pathways are shown on the right side of the cord. The autonomic afferent fibers enter the cord by way of the dorsal root which is similar to the way in which afferent fibers of the central nervous system make their entrance. However the autonomic afferents pass on through the spinal cord to the ventral horn where they make synapse with the next neurons—the *preganglionic fibers*. The axons of these neurons pass out of the spinal cord by way of the white rami and enter the autonomic ganglia formed chiefly by the cell bodies of the so called *postganglionic fibers* with which the axons of the preganglionic fibers make contact. The postganglionic fibers lead to the tissues and impulses passing over them either inhibit or excite the tissues thus innervated.

The fibers of the sympathetic division have a very wide distribution within the body. The distribution is not only extensive but the arrangement is such that it allows for a diffuse discharge of nerve impulses. It has been found that each preganglionic fiber of this division leading to the ganglia may make contact finally with not one but many postganglionic fibers.

EFFECTS OF SYMPATHETIC STIMULATION

One of the outstanding characteristics of the sympathetic division is its organization to act as a whole rather than a part. True, mild stimuli (external or internal) may have an effect on a certain part only, but chiefly the division functions in the activity of many organs and structures.

The following effects may be noted on stimulation (1) Blood vessels of the gastrointestinal tract, the gastric and salivary glands constrict (*vaso constriction*), however, the blood vessels of the skeletal muscles, coronary system and the lungs become dilated (in the brain there is no change) (2) Smooth muscles (pilomotor muscles) attached to the hairs contract (3) Heart muscle contracts more rapidly and more vigorously (4) Sweat glands increase their secretions (5) Most of the smooth muscle of the alimentary tract is inhibited (exceptions are the sphincters) (6) In the eye, the radial muscle fibers contract (dilating the pupil) whereas no effect is found on the circular fibers The same is true for the ciliary muscles (radial muscles contract, no effect on circular) (7) Retraction of nictitating membranes occurs in those animals such as birds and fish where they are developed (this is a translucent protective membrane which passes vertically across the eye) (8) The eyeball is projected owing to increased tone of the smooth muscle of the lids and orbit (9) The smooth muscle of the spleen contracts thus causing the spleen to force more blood into general circulation (10) Salivary gland secretion is inhibited or retarded (11) Alimentary tract secretions are inhibited (12) There is an inhibitory effect of the smooth muscles of the bronchi and bronchioles of the lung and they are therefore more apt to dilate (13) Glycogenolysis is accelerated in liver (and muscle) (14) Gall bladder contractions are reduced (15) There is an inhibition of the smooth muscle of the ureters of the urinary tract and the detrusor muscles of the bladder, but the internal sphincter is constricted (16) Fibers lead to the uterus Fallopian tubes *vas deferens* and other reproductive organs Some of these fibers are inhibitors and some are excitators which leads to various effects, especially during the sexual act in mammals (17) Greater secretion of the adrenal gland occurs In Figure 110 the chief sympathetic nerves as well as parasympathetic nerves are indicated

SYMPATHETICO ADRENAL RELATIONSHIP

There is a close relationship between the adrenal medulla and the sympathetic nerves so much so, that some are inclined to place them together as the *sympathetico-adrenal* system

The adrenal medulla does not receive postganglionic fibers (as one might expect, since all other organs receive post fibers) but does receive preganglionic fibers from the sympathetic division This is an exception to the rule but may be explained on the basis of development *The secreting cells of the adrenal medulla are homologous, morphologically, to the postganglionic sympathetic fibers They are both derived embryologically, from the same central mass of cells*

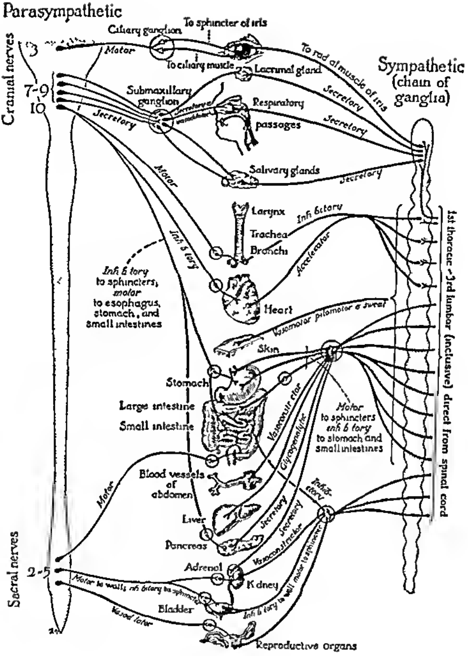


FIGURE 110

Diagram of the autonomic nervous system The cranio sacral (parasympathetic) division is shown at the left the origin relay stations, and functions are indicated The thoracicolumbar (sympathetic) division is shown at the right (the origin in the spinal cord is not shown) The fibers as they emerge from the spinal cord and enter the chain of lateral ganglia are indicated, together with the relay stations and the functions (From Greisheimer *Physiology and Anatomy* by permission of J B Lippincott Company)

The substance secreted by the medullary cells is adrenalin (or epinephrine) and it is known now that a substance similar to adrenalin is produced at the tips of most sympathetic postganglionic fibers Adrenalin has a powerful action on the body and simulates sympathetic activity It has been pointed out that 1 part of adrenalin in 1,400,000 000 parts of blood results in a definite effect Thus the evidence for close correlation between the activity of these two structures (sympathetic division and adrenal medulla) becomes stronger

EXTENT OF SYMPATHETIC ACTION

It has already been pointed out that the most significant aspect of the physiology of the sympathetic division is its tendency to act as a whole Its normal functioning has been experienced by everyone—during exercise, emotional upsets, and similar conditions When one experiences an emotional upset, such as anger or fear the whole of the sympathetic division is brought into play The heart accelerates, breathing increases and becomes easier because of dilated expanded bronchioles the pupils dilate, blood is shunted from certain areas (such as skin and alimentary tract) to supply needs of other areas that may be brought into action (such as skeletal muscle and heart) If anger leads to fighting or fear to running away, the sweat glands increase their activity in order to allow for loss of excessive heat These actions and possibly all of those mentioned previously are evident Most of the reactions which involve sympathetic discharge may be classified as emergency reactions Conditions under which the sympathetic division does discharge vigorously are those that require an overall response to ensure further proper physiological conditions or even the survival of the organism itself

This point has been demonstrated in experiments upon cats from which both sympathetic chains, except the collateral ganglia, have been removed These animals live for many months and seem to suffer no great difficulties They go about their daily routines without any striking change in behavior and continue to do so *as long as external conditions are normal* or *optimum* and as long as they are not disturbed too greatly If they meet with some stress in their environment it is found that they show a very poor exhibition of fear or anger, changes do not take place that will allow the animal to escape readily or to fight viciously If they are exposed to cold temperatures they are unable to check heat loss, thus the hair fails to rise on the back to form a greater insulation area, and the animal does not shiver in order to produce more heat to replace that which is lost Such animals show deficiencies in their ability to overcome hypoglycemia (low blood sugar), that is there

appears to be a hypersensitivity to insulin. The same condition is observed upon removal of the adrenal medulla. A still more interesting phenomenon is observed in cats which have only one side of their sympathetic system removed. If such an animal is exposed to cold temperatures, the hair on only

FIGURE 111

The reaction of a cat to coldness after its sympathetic ganglia have been removed from its right side

one side of the body (the intact side) rises while that on the sympathectomized side remains flattened out.

It was first brought to the attention of physiologists by Claude Bernard that there is in organisms a tendency to a constancy of the conditions of the internal environment (or the environment in direct contact with the cells of organisms). This has been referred to as the "steady state" or "homeostasis." The sympathetic division seems to function in maintaining this steady state.

THE PARASYMPATHETIC (CRANIAL AND SACRAL) DIVISION

In having a wide distribution of fibers in the body, the parasympathetic division of the autonomic system shows a resemblance to the sympathetic. In fact, fibers from both divisions innervate most visceral organs. The one big difference in the two divisions is that the preganglionic fibers of the parasympathetic division extend to ganglia, either on or within, the organ innervated, whereas similar fibers of the sympathetic division lie at some distance from the organ innervated. Hence, the postganglionic fibers of the parasympathetic division are relatively short.

There are two general regions from which the fibers emerge, the cranial and the sacral region (hence the subdivisions *cranial* and *sacral* parasympathetics). The cranial parasympathetic subdivision consists of four nerves that have already been studied as cranial nerves. (1) From the midbrain there is the third cranial, or ***oculomotor***, nerve which sends branches to the circular muscles of the iris and to the ciliary muscles of the eyes. When stimulated the pupil constricts (contraction of circular muscles) and the ciliary muscles contract, thus accommodating the eye for near vision. (2) The seventh, or *facial*, the ***chorda tympani*** branch of which leads to the sub-

maxillary and sublingual salivary glands, stimulation of this branch results in secretion of saliva because of direct effect on the gland (secretory) and also because of the dilation of the blood vessels in the gland (bringing more blood and substances necessary for secretion) (3) The ninth cranial, or *glossopharyngeal nerve*, supplies fibers to the parotid (salivary) gland and has the same effect on it that the chorda tympani has on the other glands, it also brings about secretion of the mucous glands of the buccal cavity (4) The tenth, or *vagus*, nerve furnishes inhibitory fibers to the heart muscle, vasoconstrictor fibers to the coronary vessels, motor fibers to the smooth muscle layers of the upper part of the alimentary tract (except sphincters), secretory fibers to most of the glands of the gastrointestinal tract, and constrictor fibers to the smooth muscles of the bronchioles

The pelvic nerve constitutes the sacral outflow and when stimulated, results in contraction of muscle cells in the colon rectum and bladder, and causes vasodilation in the external genitalia and hence erection of the penis

It was shown some years ago by means of application of nicotine that the ganglia, containing the cell bodies of the postganglionic fibers of the parasympathetic division were within or near the organ innervated There are, therefore long preganglionic fibers in this division as compared with those of the sympathetic

FUNCTION OF PARASYMPATHETIC ACTIVITY

The parasympathetic division lacks the ability to function as a whole If it did function in this way, there would be no orderliness in the behavior of organisms that is, a widespread effect would result in changes of no functional relation whatever A slowing of the heart, increased digestive activity in stomach and intestine, emptying of rectum, engorgement of genitalia, and similar activities, certainly would have no relationship This division then acts only in part and usually provides the action necessary for the occasion as it arises

It has been suggested that the cranial parasympathetics are concerned chiefly with nutritive processes or functions, that is, the seventh and ninth nerves function in the production and secretion of saliva which aids in swallowing food and which contains enzymes that hydrolyze carbohydrates The tenth nerve, or vagus, is concerned with the secretion of gastric and pancreatic juice and controls muscular activity favorable to digestive and absorptive processes in the esophagus, stomach, and small intestine

The sacral parasympathetics are said to function chiefly in the processes concerned with emptying those organs containing excretory material—

namely, the colon, rectum, and bladder There is some correlation between this subdivision and the central nervous system, that is, some control can be exerted over the emptying of these structures by way of voluntary acts Defecation and micturition are in most individuals controlled, within limits, voluntarily.

SYMPATHETIC AND PARASYMPATHETIC ANTAGONISM

Both divisions, the sympathetic and parasympathetic, innervate most tissues of the viscera resulting in antagonistic effects However, several types of structures in the vertebrate body receive only sympathetic fibers (no parasympathetic innervation), these are the blood vessels of skeletal muscles and those of smooth muscles of the alimentary tract, muscles of the ventricle of the heart, pilomotor muscles, sweat glands, smooth muscles of nictitating membrane, radial muscle fibers of the pupil, radial fibers of the ciliary muscle, thyroid gland, adrenal medulla, and uterus (especially concerned with sexual excitement)

There are also a few structures that receive fibers only from the parasympathetic division (no sympathetic innervation) These are the circular muscle fibers of the pupil, and those of the ciliary muscles of the eye, and the mucous glands of the gastrointestinal and respiratory tracts

Most of the tissues of the viscera, however, are innervated by fibers from both divisions, that is, from sympathetic and from cranial or sacral parasympathetic Whenever this occurs, it is found that one group of fibers carries impulses which are in some way antagonistic to the other in that they produce opposite effects For example, the heart (auricle) receives fibers from both divisions If the sympathetic fibers are stimulated, the beat of the heart becomes more powerful and rapid whereas stimulation of the cranial parasympathetic (vagus) retards or inhibits heart action altogether The same is true for the smooth muscle action of the intestinal tract, except that the effect of stimulating the two divisions is the reverse of that of the heart, that is, stimulation of sympathetic fibers retards smooth muscle action (but excites those of the sphincters), whereas stimulation of parasympathetic (vagus) increases activity The preceding is an instance of opposite affective action within different branches of the same nerve

An excellent example of the behavior of an animal under the influence of normal sympathetic or parasympathetic stimulation, may be shown by a cat The animal may have just finished a meal and be sitting by a warm stove quite contentedly licking its paws The pupils of the eyes are mere narrow slits Its heart rate is not very rapid (slightly better than normal rate at

complete rest) and if it were examined internally, the vessels of the gastro intestinal tract would be gorged with blood, the digestive system would be active

If suddenly, this same cat is confronted by a strange dog, the behavior be comes quite different The cat arches its back, its hair "stands on end (pilomotor activity), the pupils of the eyes are dilated the heart rate is rapid and breathing becomes deeper and as has already been noted for sympa thetic stimulation the digestive processes are interrupted, blood sugar in creases (emotional hyperglycemia), the spleen contracts, blood leaves the abdominal and skin regions to be carried chiefly to muscles and an increase in blood pressure ensures a proper blood supply to the brain

The autonomic system, then is concerned with both favorable (via para sympathetic division) and unfavorable (via sympathetic division) condi tions in its external or internal environment

It may have been noted from previous descriptions that the organs and tissues innervated by the autonomic system possess a high degree of auton omy They can carry out their functions even when the autonomic nerves are completely severed This fact, in so far as the sympathetic system is con cerned, has already been noted Parasympathectomy has not been fully accomplished but parts of this division have been severed from the tissues and organs which it innervates, and the organs have continued to function All of this evidence indicates that the autonomic system is important as a regulator but is not essential to any particular visceral action Strips of heart muscle can be isolated and they continue to contract rhythmically, the same is true of the intestinal muscle However, their action is not quite like that of tissues in their normal habitat and environment (The heart strip may beat more slowly or more rapidly)

This ability of smooth or cardiac muscle to continue contracting is not due to the presence of nerve endings in the muscle, for these can be destroyed completely or paralyzed by suitable drugs and there is also the fact that some smooth muscle of the intestinal tract contains no nerves normally, yet the muscle remains rhythmically active Thus another explanation of the con tinued contraction of smooth or heart muscle must be sought

CHEMICAL MEDIATION OF ACTION IN THE AUTONOMIC SYSTEM

Most smooth and cardiac muscles differ from striated muscles in that cer tain neurons leading to them can inhibit their action striated muscle has no nervous connection whatever that may inhibit its action The fact that cardiac and smooth muscle can be inhibited has been known for years—ever since 1845 when the Weber brothers discovered the inhibition of heart action

by stimulation of the vagus. Knowledge concerning this type of action is still vague. However, something is known about substances which, when applied to organs, may produce or simulate sympathetic or parasympathetic actions. A great step was made in 1895 by the discovery of adrenalin. It was very soon recognized that the action of this substance was very similar to that produced by sympathetic stimulation. Its action was still further emphasized by the work of Elliott (1904) who found that sympathectomized animals responded to adrenalin just as though their sympathetics were intact and had been stimulated. Later, in 1914 Dale found that on exposing an organism to acetylcholine, its responses were similar to those obtained by stimulating the parasympathetics.

LOEWI'S EXPERIMENT

In 1921 came Loewi's classical experiments, in which he proved that a substance was produced by vagal stimulation that inhibited the heart and would, if carried to another heart (not so stimulated), also bring about an inhibition of the latter.

It is not difficult to repeat Loewi's experiments. Two fresh, living (still beating) frog hearts may be isolated with their vagus nerves intact (Figure 112) and cannulae (tubes of glass, metal, plastic or other material used for

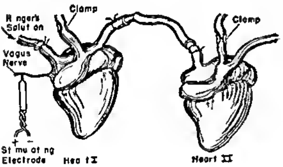


FIGURE 112

Simplified diagram of Loewi's experiment. When the vagus of frog Heart I was stimulated while Ringer's solution was passing through it to Heart II, both hearts stopped beating. Thus evidence can be presented for the production of a substance in Heart I when it is stimulated. This substance is evidently carried via Ringer's solution to Heart II.

diverting blood flow in vessels) inserted in the vessels in such a way that Ringer's solution can flow unobstructed into Heart I (via auricle) and from there into Heart II. Now, if the vagus nerve leading to Heart I is stimulated electrically, heart action is immediately affected—the heart stops beating. Almost immediately, Heart II stops beating although its vagus has not been stimulated. After a brief latency (if stimulation is not continued), Heart I begins to beat again and almost as quickly the same occurs in Heart II. A cardio-inhibitory substance seemingly is produced by stimulating the vagus

nerve of Heart I and this chemical carried in the Ringer's solution to Heart II where it is also effective. Pure blood cannot be used in place of Ringer's, it has present in it an enzyme which destroys the substance produced by parasympathetic stimulation. Loewi called the inhibitory substance produced by stimulation "vagal" substance, but the term did not last long because the same type of substance was later proven to be secreted by all parasympathetic postganglionic neurons. He also found that if, in such a heart preparation as described, the sympathetic nerves of Heart I were stimulated, heart action was speeded up; that this is evidently caused by secretion of some substance, was indicated by the speeding up of the beat in Heart II.

SUBSTANCES SECRETED BY AUTONOMIC FIBERS

The substance liberated at the tips of parasympathetic neurons was soon identified as an ester of choline, now known as *acetylcholine*. This substance is broken down rapidly into choline and acetic acid by the action of *cholinesterase*, an enzyme found in the blood stream. This prevents acetylcholine from spreading throughout the body—which could be injurious to the organism. Since it is likely that this substance is formed constantly by tonic impulses, the presence of the enzyme ensures its destruction. Many drugs affect autonomic impulses in one way or another (directly or indirectly). *Atropine* paralyzes the parasympathetic nerves or prevents the action of acetylcholine, its effect is similar to inhibition of the parasympathetics. *Eserine* (physostigmine) inhibits the action of cholinesterase and for this reason the effect of its application resembles parasympathetic stimulation because the acetylcholine would accumulate under these conditions. *Pilocarpine* action simulates that of acetylcholine.

Although adrenalin, when applied to a living system, has an effect that simulates sympathetic stimulation, it is not certain that the substance liberated at the tips of most sympathetic fibers is adrenalin itself. It was merely suggested that it is an adrenalin-like substance. Some physiologists have called the substance *sympathin*. The fact that branches of the same sympathetic nerves may produce dissimilar results (for example, inhibition of smooth muscles of the stomach but contraction of smooth muscles of sphincters) has led to much confusion and controversy and it has been suggested that the secretion of an excitatory substance (*sympathin E*) and an inhibitory substance (*sympathin I*) may be postulated, but many workers deny the existence of two kinds of sympathin.

Recently, Burn has proposed an interesting explanation for the noted dual action of these substances which are evidently formed at nerve endings and

which may cause, in some cases, stimulation, or, in others, depression of activity of tissues innervated. It has been observed, for example, that extremely small amounts of acetylcholine may actually stimulate isolated strips of heart muscle (which have been washed until they are no longer active) to contract, whereas greater amounts would inhibit contraction. In the case of intestinal muscle, whereas acetylcholine normally stimulates, very large amounts of this material will cause relaxation. Thus, while cardiac muscle is much more sensitive to acetylcholine inhibition than is the smooth muscle of the intestine, nevertheless, both tissues may be either stimulated or depressed, depending upon the amount of the substance produced when the nerves are active. Normally, however, the amount of acetylcholine in the heart is above the amount which stimulates, thus, additional amounts present when the vagus nerve is stimulated will cause inhibition. In the case of the intestine, the nerve never does produce enough acetylcholine to inhibit activity. Thus, in the living body, only a part of the action may be seen. It has been suggested that similar explanation may be applicable in the case of tissue response to adrenalin or epinephrine.

CLASSIFICATION OF FIBERS ACCORDING TO SECRETIONS

Because of the fact that a distinction must be made between production of two substances, acetylcholine and an adrenalinlike substance at the tips of autonomic nerves and because sympathetic postganglionic fibers are not always sympathin secreting (the sympathetic neurons leading to sweat glands, for example, secrete acetylcholine), it has been suggested that the various fibers be designated according to the substance secreted. Thus the following classification may be used.

A. *Cholinergic fibers*
   1. All preganglionic fibers of both sympathetic and parasympathetic divisions. This fact produces an odd situation in the case of the production of adrenalin. (the medulla of the adrenal gland which receives only preganglionic fibers from the sympathetic division is stimulated by acetylcholine to produce or secrete adrenalin)
   2. All postganglionic fibers of the parasympathetic nerves.
   3. Some postganglionic fibers of the sympathetic division (sweat glands and others).
   4. Myoneural junctions in striated muscle fibers.

B. *Adrenergic fibers*
   1. Most sympathetic postganglionic fibers.

ADDITIONAL READING

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Rosenblueth A *Transmission of Nerve Impulses at Neuroeffector Junctions and Peripheral Synapses* (Technology Press of the Massachusetts Institute of Technology and John Wiley 1950) Detailed examination of possible mechanisms in chemical transmission of impulses

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Part Four

RECEPTORS

13

Properties of Receptors

SINCE A KNOWLEDGE of the external world is based on information supplied through the sense organs of animals, a well developed receptor system is essential Humans, for example, can judge within reasonable limitations the weight of an object and its temperature, and by means of taste organs, the acidity of a solution by noting the degree of sourness

There was a time when the phrase "five senses of man" was used to express the assumption that he possesses five types of sense organs It was thought that receptors always gave sensations when stimulated by external changes in the environment Ideas on this subject changed considerably, although gradually, after the proposal and development of the theory of reflex action by Descartes during the seventeenth century There are many examples of responses to stimuli that do not involve sensation, the impulse is carried from receptors, over sensory neurons to the spinal cord, over association neurons and motor neurons to muscles, which contract Even in cases where a sensation is experienced, it often does not appear until after the reflex is completed There is also a question whether or not many receptors in mammalian bodies ever produce a sensation

OCCURRENCE OF RECEPTORS

The presence or the absence of receptor systems, in lower animals, analogous to those in man may be assumed with caution Actually receptors are found in all forms of animals and are not limited to the higher groups

The fact that an amoeba responds readily to a bright light, or a paramecium moves away from a region of high temperature indicates that the stimulus was felt It may be a form of "primitive" protoplasmic reception, but, on the other hand, there is a possibility that "receptive areas" may exist scattered over the protoplasmic mass In other more specialized forms of protozoans there are found the well defined receptors the "organelles," already mentioned (pages 26 and 50) The red "eye spot" of euglenoid flagellates is such a structure, it enables the organism to respond to light waves

The senses of lower vertebrates are, with exceptions, generally less efficient than those of man The dog however, has a much keener sense of smell

than man and the deer a keener sense of hearing, but other senses of these animals are not so acute

It is now known that many common receptors such as the eye, ear, the organs of smell and taste and cutaneous end organs are found in practically all animals from the worms through the mollusks and arthropods to the vertebrates, where they reach their greatest specialization and complexity As previously noted, they are even rather complex in some of the protozoans, and reception in coelenterates although resulting in a very diffuse response, and accomplished by means of definite structures, is comparable to that in the human skin In these organisms, the receptor is connected directly with the muscle (musculoepithelial cells) or to the nerve net The organisms have no central nervous system (or synapses) and, therefore, impulses are carried directly from receptors to effectors (muscles or glands)

Many complex receptor systems are found in the annelid worms Of course, these systems show much greater development than those of the coelenterates and as such are excellent examples of the beginning of centralization and cephalization of the nervous system Various reflexes are shown by earthworms reflexes which are possible only because of the presence of specialized receptors

CLASSIFICATION OF RECEPTORS

All of these structures, which are so modified as receptors that they can receive stimuli of a specific type can be classified and placed into one of two groups (1) the *activators*, which have nothing to do with sensations but function in reflex action, and (2) the *sense organs* which are concerned with sensations This classification of receptors is made from the viewpoint of function They can be classified also as to location (activators and sense organs together) as (1) *Enteroceptors*, or those found in the visceral organs and which lie in the mucous lining of the digestive tract and organs of respiration Ultimately, the source of stimulation may be derived from the exterior although these receptors have no direct contact with the exterior (2) *Exteroceptors*, or those which are stimulated directly from the exterior, lie close to the outer layers of the body They are the sense organs of the skin, eye, ear, nose and oral cavities (3) *Proprioceptors*, or those which are found in muscles, tendons and joints and parts of the inner ear (functioning in equilibrium), are those receptors, the stimulation for which originates in the body itself For example, the sensitive hairs in the ampullae (page 268) of the semicircular canals of the inner ear are stimulated by pressure of fluid within the canals and muscle spindles are stimulated by stretching a muscle

Muscle spindles are groups of modified striated muscle cells specialized so that they initiate impulses over nerves associated with them when the spindles are stretched

THE LAW OF SPECIFIC NERVE ENERGIES

Because it was originally set forth by Johannes Muller (1840), the Law of Specific Nerve Energies is known also as *Muller's Doctrine* Simply stated, this law means that when a stimulus is applied to a receptor (sense organ) it gives rise to a very specific sensation This was realized from observations for some years before Muller, but physiologists were not certain whether the specificity was due to peculiarities in the type of energy or to peculiarities in the end organs themselves Muller believed the latter view to be correct, and he evidently took into consideration the neurons as well as the actual sense organs However, today there is an inclination to look upon the specific quality of a sensation in consciousness as dependent upon the association areas of the cerebral cortex, the end organs and the conducting neurons merely receiving the stimuli and carrying the impulse to the center To be sure, each sense organ itself is important in the reception of a certain type of stimulus and, therefore, enters into the specificity of the nature of the sensation along with the brain center involved This is true especially under normal circumstances Thus, the eye receives light stimuli the ear sound waves, and the taste areas and possibly the olfactory areas, chemical stimuli These stimuli when applied to the proper organ are referred to as *adequate stimuli* However, it has been said that, if it were possible to cut the optic and auditory nerves at their peripheral ends, and to unite the optic nerve to the auditory end organs, or the auditory nerve to the visual end organs then upon stimulating the eye with light, sound would be heard, or upon stimulating the ear with sound vibrations, light would be seen In other words, the energies set up within the center of the cerebrum always result in the same sensations, no matter what type of stimulus started the impulse wave in the beginning

Some of the evidence in favor of the Law of Specific Nerve Energies would include the common sensation that most individuals have felt when our sense organs have been stimulated by unnatural means For example, a blow on the eye in the dark will set up impulses in the optic nerve One is said to 'see stars Actually, the impulses which have been aroused mechanically are carried to the center which is specific for light sensations A 'ringing in the ears is a common experience, especially at the onset of fever, or after the taking of certain drugs The ears, in these cases, are not

stimulated by sound waves, but the temperature or the drug has such an effect that impulses are set up in the auditory nerves—hence, the ringing sound. These types of stimuli are said to be *inadequate stimuli*.

DIFFERENCES BETWEEN SENSATIONS

Different sensations are absolutely distinct in consciousness of them. Sight, smell, taste, sound, and touch are never confused, they can be separated in one's consciousness. These different sensory impressions are not referred to the brain but to the sense organ stimulated, that is, taste is referred to the tongue and sound to the ear. This difference between one sensation and another which separates them in consciousness is referred to as *modality*. Quality can also be distinguished within a modality. This simply means that in sound, for example, one can judge between a tone of low or high pitch, or in colors, between blue, green and others. However, the quality of one modality cannot be compared with that of another. For example, one cannot say that this sound is of higher pitch than this taste is sweet. Each sensation, therefore, possesses a modality that is absolutely specific for it and the quality within the modality can be ascertained. *Intensity* of sensation can also be distinguished within a certain modality, such as bright and feeble light of the same color or loud or weak sound of the same pitch.

THE PSYCHOPHYSICAL LAW OR WEBER'S LAW

The intensity of a sensation increases with the strength of the stimulus. Since conscious sensation is not measurable in physical terms, a "just perceptible difference" must be used as the unit of measurement. The strength of the stimulus is measurable in degrees of temperature, grams per square centimeter pressure, and similar physical means. Actually, the number of impulses passing from a receptor over its neuron may be determined experimentally and it may be found that the number of impulses per unit of time is proportional, within limits, to the strength of the stimulus. Thus, although a few impulses pass with a weak stimulus, many more pass as the stimulus is increased. Weber (1846) was the first to make the observation that a *change in the strength of a stimulus necessary to produce a perceptible difference in sensation is proportional to the intensity of the stimulus already acting*. This holds true only for stimuli of moderate intensity. If a weight of 30 g is placed on the tip of the index finger, it requires the addition of 1 g to this weight to result in a perceptible difference; that is, the extra gram can be felt as an added weight. If less than 1 g were added, the difference would not be felt. If 60 instead of 30, g were placed on the index finger, 2 g would have to be added to produce a sensation of difference, if 90, 3 g

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must be added and so forth up to the physiological limit (about 1000 g) In the case of touch and pressure then the ratio is 30 1 for sound it has been found to be 9 1 and for light 120 1

ADAPTATION

Usually a decrement in response to a stimulus is referred to as fatigue whereas the phenomenon is rather one of adaptation One seems to be come accustomed to a stimulation It is true that fatigue may enter into the picture but for the most part in reference to action of the sense organs one becomes adapted to a stimulus As previously stated (page 136) a stimulus applied to a sense organ results in a volley of impulses which proceed over the nerve to the central nervous system These impulses last for a brief space of time but if the stimulus be continually applied it is found that the rhythmical discharges of impulses diminish and may disappear com pletely Stimulation of touch receptors for example by application of a disc of known weight to the skin surface is followed by a burst of impulses which continue for from 0 1 to 0 2 sec but disappear entirely by the end of 0 5 sec although the same pressure is maintained continuously on the disc If slightly greater (or lesser) pressure is now applied to the skin another volley of impulses follows which ceases at about the same time as the first In the same way one becomes adapted to odors to the ticking of a clock and to the contact of clothes Even the retina becomes accustomed to a stationary object and in order to perceive it best the eyeballs are kept mov ing constantly (though so slightly as to remain unnoticed) in order that the end organs may be stimulated intermittently

If this phenomenon were one of fatigue it should be more evident with the stronger stimulus but actually the condition is most evident with weaker stimuli that is a strong odor is detected for a longer time than a weak one If this were a fatigue phenomenon it would appear sooner as well as being more evident with the stronger stimulus Another argument against this being a state of fatigue is that the rapid decline in frequency of impulse discharge is not affected by a lack of oxygen fatigue appears most rapidly in its absence Adaptation is a property common to receptors and is evidently a protective one in the case of touch reception and the like that is certain receptors after responding to a stimulus and conveying impulses over the nerves of the C N S become adapted to that stimulus and are soon again ready to respond to a second similar stimulus On the other hand receptors for pain adapt very slowly and so a harmful stimulus might be detected for a long period of time If adaptation to painful stimuli occurred as rapidly as that for tactile sensation one might by conscious effort with

stand the initial brief period of sensation and adaptation, and then the unfavorable contact might be continuously maintained without further sensation Thus, great harm might be done to the body Adaptation differs considerably with different end organs, and thus some adapt themselves readily to their specific stimulus, whereas others are able to respond for minutes or even hours

ADDITIONAL READING

Fulton, J F, *Textbook of Physiology*, 16th ed (Saunders, 1950), pp 292–300 Receptor properties

14

Cutaneous and Visceral Receptors

THE SENSE OF PRESSURE OR TOUCH

THE RECEPTORS which function in the perception of touch (or pressure) are sometimes referred to as *tangoreceptors*. Protoplasm itself is sensitive to pressure changes or touch. In the lowest forms, such as protozoans and sponges, therefore, no special structures are needed for this type of reception, at least complicated receptors are unnecessary. In coelenterates touch reception is very important. The hydras, for example, have no means of sensing the presence of a foreign body except by touch (unless possibly partly by chemical sense). They cannot see their prey, but if a daphnia or some similar food morsel should happen to touch the tentacle of a hydra there is an immediate response in the latter brought about by stimulation of sensory cells lying in the ectoderm, which results in the entanglement of the daphnia in the tentacles of the hydra. The nematodes, flatworms and echinoderms are all very sensitive to contact. The respiratory papillae on the surface of starfish are especially sensitive. Much of their sensitivity is undoubtedly the result of stimulation of bare nerve endings as well as specialized end organs, some of these latter being provided with flagella. The annelid worms not only have bare nerve endings permeating the outer regions of the skin but also have sensory cells specialized for contact (Figure 113). Hairlike structures penetrate to the outside of the cuticle, reflex activity resulting when they are stimulated. The anterior segment (prostomium) of the earthworm is especially sensitive and it is found that many nerve ending pervade this region.

The arthropods have lost their surface sensitivity for the most part because of their chitinous exoskeleton. This difficulty is overcome by the presence of very sensitive tactile hairs. When an object makes contact with these hairs, which protrude between segments and joints, pressure is brought to bear on sense cells at their base, resulting in the passage of impulses over the sensory neurons leading from the organ. This is similar to touch reception in higher animals, the hairs of which have sensory cells at their base which are activated by pressure. Animals belonging to this group (crayfish, lobster, insects and other arthropods) also have very specialized organs for touch in their antennae. It is a common sight to see an insect

or a crustacean creep slowly along waving its antennae in all directions, stopping when the antennae make contact with an object, and then proceeding again

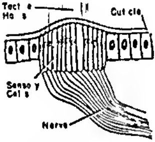


FIGURE 113

A tactile sense organ in the outer skin layer of the earthworm

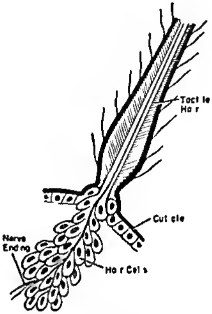


FIGURE 114

Tactile hair of an arthropod

It was not until 1882 that a division of the cutaneous end organs in man and other vertebrates into heat, cold, and pressure spots was made; it was even later before a fourth type of sense organ in the cutaneous region—*pain spots*—was discovered

If the hair is touched in any way to bring pressure against its endings, the resulting sensation is that of touch. The hairs exaggerate the pressure of any object with which they come in contact because they act as levers. For example, brushing lightly a hairy surface of the body with cotton can be

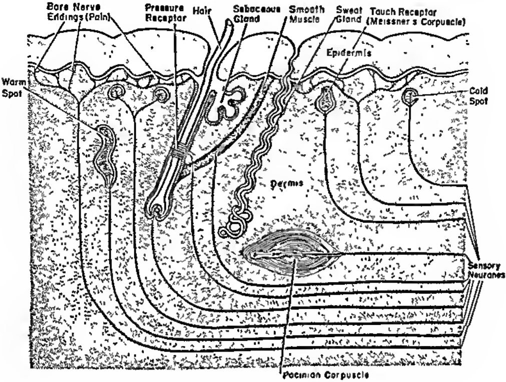


FIGURE 115

Section through skin showing the various receptors in the cutaneous and subcutaneous regions

sensed quite readily. If the hairs are shaved, the sensitivity is greatly reduced. Cat's whiskers (vibrisae) and the whiskers of other animals of this type are very useful as touch organs. All three of these structures (Meissner's corpuscles, bare nerve endings, and nerve endings surrounding hairs) are concerned with pressures of less than 10 g. If the pressure is greater than this, other sense organs (deep pressure) are brought into play. The *Pacinian corpuscle* functions in this latter category. As seen from the figure, it is laminated and has an appearance quite similar to an onion which has been cut in cross section or longitudinally. These corpuscles are often near the surface and are easily located in the paw of a cat. They are found chiefly in muscles, tendons, and joints and in this capacity behave as proprioceptors (page 186).

An instrument known as an *esthesiometer* is often used to ascertain the sensitivity of the skin to touch It usually consists of a simple wooden holder to which bristles (or other fibers) can be attached By calculating the number of grams necessary to bend hair of various thickness it can be determined by trial the precise hair that will just elicit a sensation of touch when bent at a certain angle (The pressure in grams necessary to bend the hair is known) The ability to detect touch varies considerably over the body surface

LOCALIZATION AND DISCRIMINATION

When the skin of an individual whose eyes are closed is touched he can with a certain degree of accuracy recognize the location of the stimulus The ability to localize sensation of touch in this way varies at different points on the skin being much greater for example when the stimulus is applied to the lips or the tip of a finger than when applied to the thigh or the back

The ability to discriminate between two points stimulated at the same time (that is the ability to feel two distinct sensations) depends upon the distance between the two points which distance varies with the region stimulated The discrimination test is sometimes called the compass test because usually a pair of compasses is used and the least distance found between the compass points at which they may be sensed as two distinct sensations is a measurement of the acuity for that particular region Figure 116 illustrates the ability to discriminate at different areas on the body

The power to localize and discriminate appears to decrease from the more distal portion of a limb to the proximal regions It may also be noted that this ability appears to decrease from the more movable part of a structure to the less movable For example discriminative power is greatest near the lips which are quite movable but decreases considerably near the ear region A similar relationship applies to the finger tips and shoulder and

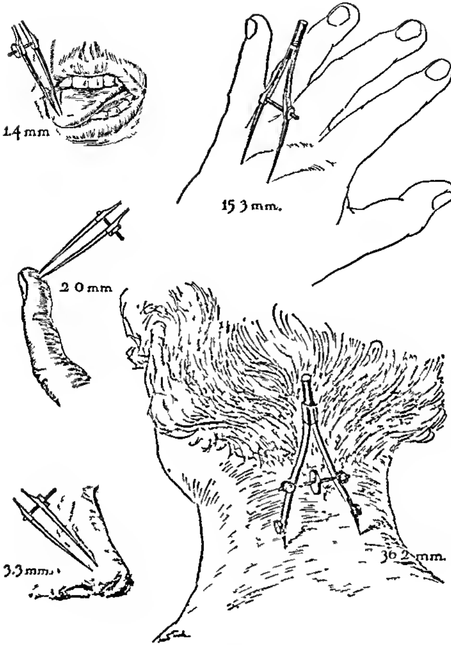


FIGURE 116

Variations in sensitivity in two point or spatial discrimination The distance between the compass points indicates the sensitivity in different regions The tip of the tongue is most sensitive, the back of the neck least sensitive (From Greisheimer *Physiology and Anatomy*, by permission of J B Lippincott Company)

FIGURE 117

Illustrating Aristotle's experiment in which a pea or some other object is rolled on the palm of the hand by means of crossed fingers. There is an illusion of touching two separate objects.

PROPRIOCEPTORS OF MUSCLES, TENDONS, AND JOINTS

The proprioceptors furnish information as to the position and movements of the limbs and body; they function also in maintenance of posture. It has been found that in some of the nerve trunks one third to one half of the fibers are afferent and carry to the central nervous system impulses which originate in the subcutaneous regions and in receptors within the muscles (stretch receptors and the like). By reflex action, certain muscles, especially those concerned with posture, contract in a coordinated fashion to produce smooth and effective movements or to maintain posture. The receptors which function in such activity are sometimes referred to as *kinesthetic*. These receptors escaped notice for years because, for the most part, one is not conscious of any sensations elicited by the stimulation of these receptors (except for movement of the body in space and for direction of movement). They respond to mechanical stimuli, pressure or stretch. Several end organs have been found in muscles and tendons which may be classified as proprioceptors as follows. (1) The *Pacinian corpuscles* are found in muscles, tendons, and joints as well as in deep subcutaneous regions. (2) *Muscle spindles* (Figure 118) consist of a bundle of three to ten modified striated muscle fibers enclosed in a layer of connective tissue. These fibers are smaller than the usual striated muscle fiber and have a greater number of nuclei and coarser striations. When a muscle is stretched, afferent nerve fibers leading from the spindle are stimulated and carry impulses to the central nervous system which return via motor fibers to the muscles, causing the latter to contract. The degree of contraction depends upon the degree of stretch. Thus any tendency of the back or leg muscles to stretch because of the body bending unknowingly, or tending to bend to one side, results in an immediate volley of impulses to these muscles which causes them to

contract and, hence, to maintain the posture of the individual (3) In the tendons are found *Golgi corpuscles* which consist of tendinous fibers, surrounded by fibrous connective tissue The effective stimulus for these structures is tension (4) *Bare nerve endings*, many of which are found within muscles and joints, play a part in the mediation of deep pain

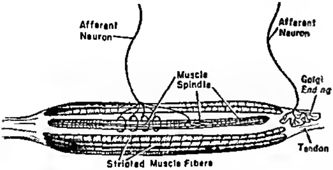


FIGURE 118
Stretch receptors in muscle and tendon

THE TEMPERATURE SENSE

Many animals are sensitive to changes in temperature and most of them have special receptors associated with these changes Protozoans will turn away from areas of high or extremely low temperature and seek more moderate temperatures It is evident from this that protoplasm is sensitive to temperature change and, since there are no special receptors in the lowest forms, the latter must depend upon direct protoplasmic stimulation Temperature sense is well established in the insects and some of them are found to be as sensitive to heat or cold as are mammals In higher animal forms, both invertebrates and vertebrates, two types of end organs concerned with temperature changes are found, one type for warmth and the other for cold

TEMPERATURE SENSE ORGANS

The end organs of temperature sense and their locations in the skin can be mapped out as cold or warm spots in the same way that touch spots are mapped out, but by using a cold metal rod for ascertaining cold and a heated rod for warm spots It is found that the areas sensitive to warmth are not the same as those sensitive to cold One would expect, therefore, to find two different types of end organs Because of conduction, temperature differences can be felt almost anywhere on the skin, provided the metal rods are held in contact with the skin long enough In Figure 115 (page 193) it is seen that the end organs (*Ruffini's endings*) for detection of warmth lie much deeper than those for cold (*Krause's end bulbs*) These end organs are not equal in number On the forearm cold spots number from thirteen

to fifteen, and warm spots one or two, per sq mm In exposed parts of the skin, such as the face, there are very few cold spots On the other hand, on certain mucous membranes there is an absence of warm spots The mucous membranes of the throat are of this type and for this reason one can drink fluids much hotter than the skin can bear

ACTION OF HEAT AND COLD ON END ORGANS

In spite of the differences in structure and location of these end organs, there is some relationship between the sensations of heat and cold Both types of receptors are actually dependent upon heat exchange for their adequate stimulus It may be said that heat is the actual stimulus in both cases, since cold is not a positive quantity, but is caused by an absence of heat The stimulation of warm or cold spots depends upon whether the temperature at the surface of the skin (external environment) is greater or less than that of the subcutaneous layers

A *temperature gradient* exists when there is a difference in temperature between two bodies The gradient is always directionally from the warmer to the colder area, since heat energy passes in that direction The greater the difference in temperatures, the greater the gradient and the greater will be the warming or cooling effect

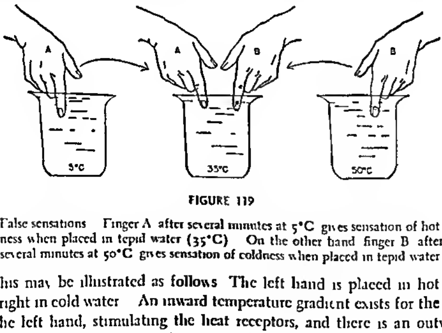


FIGURE 119

False sensations Finger A after several minutes at 5°C gives sensation of hotness when placed in tepid water (35°C) On the other hand finger B after several minutes at 50°C gives sensation of coldness when placed in tepid water

This may be illustrated as follows The left hand is placed in hot and the right in cold water An inward temperature gradient exists for the skin of the left hand, stimulating the heat receptors, and there is an outward gradient in the skin of the right hand which has a cooling effect because of the loss of heat from the cold receptors Gradually these sensations disappear This is owing partly to adaptation and partly to the fact that, as

the skin temperature changes in order to approximate the temperature of the environment, the gradient becomes less and less extensive, and, therefore, the stimulus becomes weaker and weaker. Now, if both hands are placed in tepid water, the temperature gradients are reversed. The skin of the hand that has been in hot water is warmer than the environment (tepid water), and so the cold receptors are stimulated. The skin of the hand that has been in cold water is cooler than the tepid water and thus the warm receptors are stimulated.

The temperature sense seems to be most apparent on the anterior surface of the arm, and the surface of the abdominal region, chest, nipples, and nose. It is less marked in such areas as the scalp, face, and hands. The sensitivity of the temperature end-organs varies greatly with the previous treatment of the skin and its present condition, but it is found to be most acute at ordinary skin temperatures, 27 to 32 degrees C.; in this range the skin is sensitive to a change of 0.2 degree C.

At very hot or very cold temperatures the skin loses its acute sensitivity. In fact, extreme temperatures are thought by some to affect different structures from those already mentioned. Evidently, the sensation of extreme heat is due partly to temperature sense and partly to pain.

It is rather difficult to explain some of the cold and warm sensations produced on the surface of the skin when neither a cold nor a warm object has come in contact with it. For example, menthol gives rise to a sensation of coldness whereas carbon dioxide causes one of warmth.

PAIN

The pain sense seems to warn of danger in that it reveals the presence of injurious abnormal conditions.

Overstimulation of any sense organ such as that produced by loud noises and great light intensities, for example, results in painful sensations. At one time it was thought that pain was a common sensation produced by intense stimulation of other kinds of end organs. However, this belief is in violation of the doctrine of specific nerve energies. More recently, the discovery of pain receptors, lying in close conjunction with Meissner's corpuscles, has offered a possible explanation for the observation that strong pressure on the skin in a region sensitive to touch may cause a painful sensation. If the existence of pain receptors in conjunction with other end organs in the body could be proven, then painful sensations experienced with excessively strong stimuli could be explained.

Certain definite pain spots can be rather exactly located on the surface of the body; but pain sensations are produced also in deeper tissues and organs.

These pain spots can be located by means of a needle and do not coincide with other end organs (such as those of touch heat, cold) The skin has the greatest distribution of pain spots, an incision in the cutaneous region is much more painful than one made in deeper organs On the average, there are more than one hundred pain spots per sq mm of skin surface These specific end organs are evidently bare nerve endings, there do not seem to be any modified structures for reception of painful stimuli The cornea and glans penis are both richly supplied with bare nerve endings but contain no modified end organs It should also be noted that pain nerve

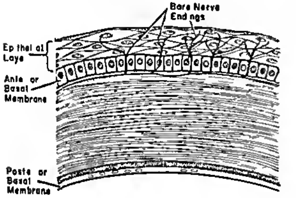


FIGURE 120

Section through cornea showing pain nerve endings in epithelial layer

endings are not specialized in their type of reception but may be acted upon by many kinds of stimuli such as mechanical thermal, and electrical It has also been found that these naked nerve endings are present in especially large numbers in small veins and may be responsible for the extreme pain suffered in phlebitis or inflammation of the veins

Three types of pain are recognized according to location (1) cutaneous, (2) deep pain (muscles, tendons and joints), and (3) visceral pain The first two are to a certain degree similar in nature, except for position The latter is rather difficult to explain

Visceral Pain

Just as painful stimuli applied to the surface of the skin warn animals of danger, stimuli of the same sort give warning to abnormalities within the visceral organs Painfulness may compel rest and in this way favor the healing of an injured or diseased organ However, the painful sensations resulting from stimulation of a visceral organ are not always associated with that organ in consciousness, but may be referred to some other region of the body This is called *referred pain* A satisfactory explanation of this

phenomenon has not been made but it is known that the afferent (or sensory) neurons, which lead from the viscera make their entrance into the cord in close association with afferent (or sensory) neurons from the skin Both of these neurons end close to cells whose axons form ascending tracts for impulses arising from stimulation of the skin It is thought, therefore, that a painful sensation aroused by visceral stimulation is projected to that part of the body surface whose afferent neuron pathways are most closely associated with those of the visceral organ

In Figure 121 are shown the areas to which pain sensations from various visceral organs are referred For example liver and gall bladder pains are felt in the region of the right shoulder and it is found that sensory neurons from the shoulder area and sensory neurons from the gall bladder enter the cord at the same level Pain as a result of constriction of the ureters is felt in the groin region In fact most visceral sensations are painful no matter what their origin There are two common causes of visceral pain (1) *prolonged contraction* of smooth muscles as found in spasms of the stomach and intestine and (2) *stretching* of internal organs such as the gall bladder and gaseous extension of the intestine

Headache

The exact cause of headache is not known It is believed that the surface of the brain and the small blood vessels are insensitive to pain However, large blood vessels within the meninges and at the base of the brain may contain receptors which are stimulated by distension of the vessel walls this may be the cause of headache Traction or distension of the membranes themselves may be contributing factors Such a condition could be produced by any agent causing a disturbance in the fluid balance between the blood and the cerebrospinal fluid Migraine as well as common headache may be explained by this upset During the period at which one suffers from migraine, there is a noticeable water retention (fluids are not removed from the body by the usual means that is, kidney and skin), which would result in a greater pressure in blood vessels and within the subarachnoid space as well as the ventricles of the brain Headaches found in persons suffering from brain tumor are evidently caused by an increase in the intracranial pressure, or pressure on the nerves or on the meninges Sometimes headache appears as a referred pain such as that suffered when ice cold drinks or ice cream are swallowed too hurriedly Here the effect is evidently on sensory branches of the vagus coming from the esophagus The pain is referred to the front part of the head which is innervated by the trigeminal or fifth cranial nerve

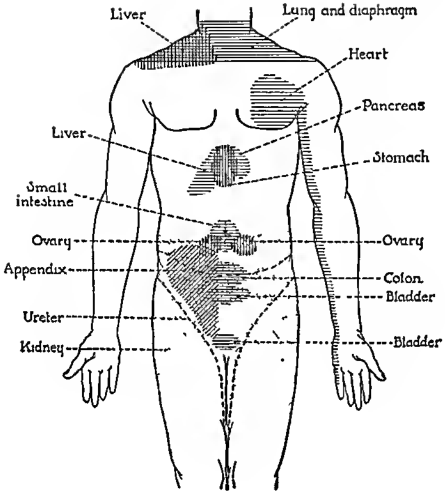


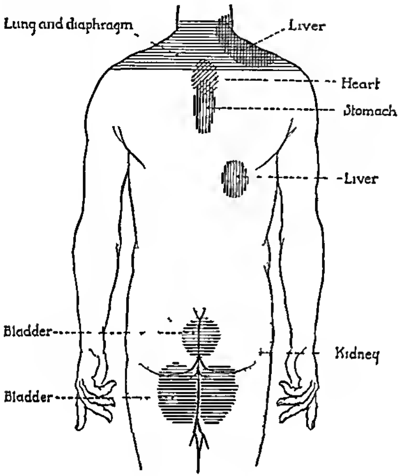
FIGURE 121

Referred pain Above, anterior view, on facing page, posterior view The cutaneous areas to which pain in the various organs is referred are indicated (From Greisheimer *Physiology and Anatomy*, by permission of J B Lippincott Company)

Hunger

Hunger is a definite sense as contrasted with appetite which should not be classified as such The latter is merely a state or condition during which food would be acceptable and it is especially aroused in a person subjected to pleasing odors and tastes It may be very specific for certain types of food and may continue even after hunger has disappeared

Hunger sensations are very disagreeable and occur intermittently The sensation has been found to coincide with waves of contraction that travel over the entire empty stomach, which is usually in an extreme state of tonus



Normally, when food is present in the stomach only the pyloric region shows contraction waves Perhaps the great tonic condition plus the waves of contraction and the fact that the contractions involve the whole stomach are the factors concerned in producing hunger No painful hunger sensations are felt in a person whose stomach is full' or partly so although contraction waves pass over the organ continuously, however, under these conditions tonus of the smooth muscles in the walls of the stomach is not very great Evidently, there are receptors imbedded in the walls which are stimulated by the types of contraction described above

Hunger pangs may last for several minutes and then disappear to return at a later time Eventually, the effect seems to wear off persons who have starved over long periods of time have reported that after a few days they no longer suffer from such pain

The function of hunger is obvious, and animals suffering from it will seek and partake of food The taking of food is a reflex with hunger as its basis Hunger becomes rhythmical because of rhythmical habits The tendency is

to become hungry at about the same times each day because a habit of eating at those particular periods has been formed If one does not eat at the regular period but waits for two or three hours, weakness, headache, nausea, and general discomfort set in

Thirst

Thirst sensations are experienced when the mucous membranes of the throat and mouth tend to become dry or partly so Evidently, there are receptors in this region which are affected by dryness This condition is brought about generally by a reduction in water intake which in turn causes the blood to draw upon the tissues of the body (including the salivary glands and mucous glands of mouth and throat) for water Thirst can actually be relieved by injecting water directly into the veins, it need not be swallowed and absorbed Contrary to reports of those who have suffered from hunger and thirst thirst sensations are never alleviated and sooner or later lead to mental breakdown The desire for water is a property of all protoplasm Species of animals found in water need not have special structures In such animals, however, as earthworms and frogs, which depend entirely or to a considerable extent on absorption of oxygen through the skin layers, sensations akin to thirst must come into play to force them to seek moisture (reflexly), or at least to seek a location where the moisture they already have will not be lost It is highly probable that the thirst mechanism, including the end organs specialized for thirst, evolved from such mechanisms as are possessed by these lower forms

ADDITIONAL READING

Best, C H, and N B Taylor *Physiological Basis of Medical Practice* (Baltimore Williams and Wilkins 1950), ch 64 Cutaneous and kinesthetic sensations

Fulton J F, *Textbook of Physiology*, 16th ed (Saunders 1950), pp 300–314 Somatic sensations

15

Chemoreceptors

All animals react to chemicals in their environment In the case of animals that live in water, chemicals must be soluble in the environment in order to be detected In the case of terrestrial forms they must be soluble in saliva or the watery layer of the mucous membrane in the mouth, or dissolved in the blood Even protozoans, such as *Amoeba* or *Paramecium*, have a very delicate chemical sense An amoeba responds readily to the presence of food in the environment and will move toward it and engulf it, a paramecium will do the same and will respond positively to very weak acid solutions Paramecia, if placed under a cover slip on a microscope slide to

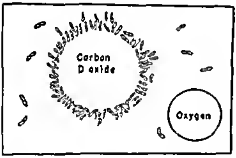


FIGURE 122

Paramecia reacting to a bubble of carbon dioxide gas Note their apparent avoidance of oxygen (after Jennings)

which is also added a bubble of carbon dioxide, will collect around the margin of the carbon dioxide bubble Presumably the weakly acid reaction of the water at the margin is sufficient to "attract" the organisms This "chemical sense" is fairly generally distributed throughout the invertebrates

The arthropods and vertebrates are very well specialized Butterflies have organs on their tarsi (feet) by which they can detect very dilute concentrations of substances, such as sugar If the tarsus is placed in dilute sugar water, a butterfly responds by uncoiling its long tongue or proboscis (which, when curled up looks like a watch spring) and placing it in the solution It is said that the tarsi of butterflies can detect a concentration of sugar two hundred and fifty times more dilute than that of the weakest solution that can be detected by the taste organs of humans The sense of smell of butterflies is also very keen

In amphibians and fishes, taste organs are found all over the surface of the

body, thus the catfish can detect meat juices in contact with the sides of its body.

COMMON CHEMICAL SENSE

As has been pointed out previously, all protoplasm is acted upon by chemicals in the surrounding solution, especially if their concentration is high, the response of the organism indicates the possession of a chemical reception. Those mucous surfaces in man that are more or less exposed to the outer environment are sensitive to many chemicals. In some cases, the sensitivity may be owing to an osmotic effect, in others the effect is truly chemical. The nasal cavity, mouth, pharynx, anus, and vagina, structures lined with a mucous membrane are often irritated by contact with chemicals. A sensation far different from taste or smell is perceived, it is usually one of irritation which may result in an intense desire to scratch, to cough, or to sneeze. The response in such cases is always a protective one.

CHEMORECEPTORS IN AORTIC AND CAROTID BODIES

In mammals, there are several types of chemoreceptors. One type that is mentioned again (page 369) in the discussion on circulation is that which is found in the aortic and carotid bodies. These receptors are stimulated by a low oxygen tension or oxygen lack in the blood (anoxia and anoxemia). These receptors function in association with the respiratory center under conditions which bring on anoxia conditions existing at high altitudes or in environments where much of the oxygen has been replaced by other gases. They may be affected by high carbon dioxide tensions, but under normal conditions the respiratory center of the medulla regulates this to such an extent that the carbon dioxide tension in the blood is far below that which would stimulate the carotid or aortic bodies.

OLFACTORY SENSE IN MAN AND OTHER ANIMALS

Man can detect chemicals which are volatile enough after reaching his nasal cavity through the air, to come in contact with specialized olfactory structures (Figure 123). Both taste and smell are excellent examples of chemoreception. From experience, one usually looks upon smell as being conveyed through air and taste through water. Actually, in both cases the stimulating substances are conveyed to the receptors by water, that is, substances must be in solution when they reach the end organs of taste in the mouth or those of smell in the nasal cavity. Usually the substances one smells are very volatile chemicals whereas those one tastes are not so volatile

However, most of the so called 'tastes' are mixtures of both It is true that the substances carried through air (the more volatile) are more potent in their action than those carried through water, and so, much lower concentrations of the former are needed to stimulate In other words, the sense of smell is a rather powerful one There are many animals with a sense of

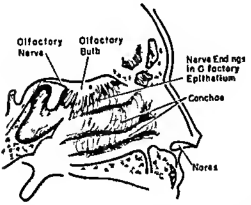


FIGURE 123

The nasal cavity as viewed from the septum showing the olfactory region and the conchae formed by the turbinate bones in the respiratory region of the cavity

smell much more acute than that of man Thus dogs cats, and some insects and crustaceans all have a very keen sense of smell The male moth can detect a female miles away the sense organs of these insects are found in the antennae

There are two areas or regions in the human nasal cavity—the respiratory and the olfactory The *respiratory area* or region is richly supplied with blood (hence the red color) and has many free nerve endings surrounding the epithelial cells This part of the nose is very sensitive to irritating chemicals such as ammonia acid vapors and ether Usually these substances do not enter the uppermost region of the nasal cavity (olfactory region) because they give rise to a reflex holding of the breath when they come in contact with the nerve endings and thus serve to prevent damage to these areas Impulses are carried by the trigeminal nerve, but the sensation is one of irritation and not a true odor

The *conchae* of the respiratory region are especially vascular and at the same time erectile During colds allergic reactions and the like, they become quite swollen because of irritation Certain drugs will bring about a reduction in the swelling The high vascularity of this region functions in the moistening and warming of the air as it goes to the lungs

The *olfactory area,* innervated by the olfactory nerve, occupies about 250 sq mm of surface on each side in the uppermost part of the nasal cavity It is yellowish brown in color as compared with the reddish respiratory area Because of its situation in order that an odor may be detected most effi

ciently, the air must be drawn in as short sniffs, which results in a stirring action that brings about a mixing of the air with that in the upper nasal cavity.

The olfactory epithelium consists of three types of cells: (1) *basal cells*; (2) *epithelial supporting cells*; and (3) *olfactory cells* (Figure 124).

In spite of their perfection in sensing odors, the olfactory cells are very simple and primitive. It is not understood how the end organs function in recognizing numerous odors. The sensory cells responsible for reception of odors consist of nerve cells from which sensory hairs protrude. These hairs are actually protoplasmic protrusions of dendrites of the modified nerve cell.

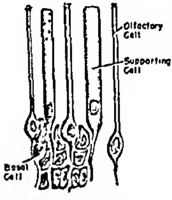


FIGURE 124

Cells of olfactory epithelium, slightly separated to show their structure and position

It has been suggested that the virus of poliomyelitis may gain entry by way of the olfactory bulb (Figure 123); investigations have been carried out in which the olfactory epithelium of monkeys has been destroyed by zinc sulfate in an apparently successful attempt to prevent entrance of the virus. However, this view is still controversial.

Degree or acuity of olfaction can be estimated by use of Zwaardemaker's ol factometer (Figure 125)

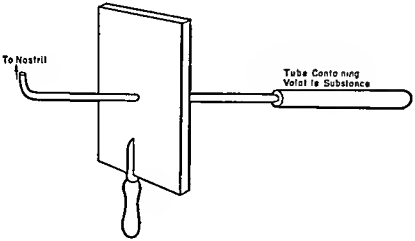


FIGURE 125

The olfactometer as devised by Zwaardemaker The solution to be tested is placed in the cylinder, the smelling tube is applied to the nostril

Acuity of the olfactory sense in women and children is said to be superior to that in men, it varies considerably in different persons, in that some have exceptional keenness, whereas others are completely deficient This sense adapts itself quite readily Foulness in the air of a room may not be detected by persons who have been in the room for some time whereas it is detected immediately by one walking in from the fresh air outside One can be come adapted to one odor without affecting his ability to detect another of a different sort The sense of smell recovers from the adaptation quite readily

Many substances which act upon olfactory endings have peculiar char acteristics in that their action may be of two types—the effect on the end organ, and the effect on other nerve endings Such volatile substances as already mentioned (ammonia, sulfur dioxide, and acids) besides stimulating the nerve endings of the olfactory area to receive and sense their peculiar odor, also stimulate bare nerve endings (and possibly other tactile endings) The two sensations result in the "pungent" effect which these substances have

Many attempts have been made to classify odors and although no entirely satisfactory classification has been suggested, Henning's can be given as

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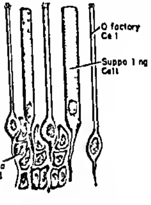

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The fact that there is usually no direct contact between the incoming air and the olfactory epithelium is of considerable benefit Several advantages are (1) the cold air of the external environment does not come into contact with the olfactory region and so can do no damage to it (2) if the air should be dry the fact that no contact is made with the sensory cells protects them from drying (3) substances such as ammonia acetic acid and noxious fumes of various types do not come into direct contact and hence do not damage the area and (4) bacteria and various foreign particles which might do harm are not so apt to reach this part of the nose

Acuity of the Olfactory Sense

The concentrations of chemicals necessary to excite the olfactory endings are very dilute For example 0.01 mg of mercaptan (an organic sulfur compound) in 230 cubic meters (or .00000004 mg in 1 liter) of air can be detected The quantity in direct contact with the end organs of the olfactory epithelium would be much smaller Ether and oil of wintergreen can be detected in concentrations equal to 0.0005 mg per liter of air musk in concentrations of 0.00012 mg per liter and vanilla 0.0001 mg per liter

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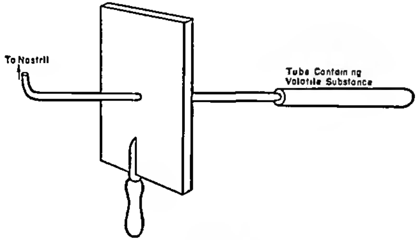

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typical He distinguishes the following types (1) flowery, as in roses and violets, (2) fruity, as in lemons and oranges, (3) spicy, as in nutmeg and cloves, (4) resinous, as in frankincense, (5) putrid, as from hydrogen sulfide and carbon bisulfide, (6) burning, as in tar

SENSE OF TASTE IN MAN AND OTHER ANIMALS

Taste is a sense upon which the animal may depend in order that proper diet may be obtained It is not simply a luxury bestowed upon higher animals so that food may be enjoyed to a greater extent, but under some circumstances it may be a valuable guide in the selection of substances necessary for the life of animals In recent years it has been shown that some animals (rats and humans) depend upon it for maintenance of constancy within the internal medium, as well as in nutritional selection Rats suffering from dietary or endocrine deficiency will choose those substances that will benefit them the most by correcting the deficiency It is found that an adrenalectomized rat will select sodium chloride solutions which will support the life of the animal, since it would die within a few days without the cortical hormone of the adrenal gland which regulates sodium chloride metabolism Cases of adrenal cortex insufficiency have been reported in children who managed to keep themselves alive temporarily by selecting sodium chloride (by taste) in their diets A rat with vitamin deficiencies will select those substances containing the necessary vitamins, but rats if their nerves of taste are destroyed, will be unable to select, and will eventually die This is one indication of the importance of taste to the life of an animal

As brought out in an earlier discussion, taste is usually so linked with the sense of smell that it is often difficult to distinguish between the two Flavors are dependent upon both of these receptor systems

In some fish, taste end organs are found all over the body, in insects, on the tarsus (foot) and the antennae In man, they are found in the mouth region, chiefly on the tongue However, they are found also on the pharynx, soft palate, epiglottis and, in the infant, on the cheeks, lips, gums, and under surface of the tongue

Taste Buds

The taste buds are found chiefly on the tip, sides and posterior region of the upper surface of the tongue They appear as oval bodies, each about 8×40 microns in size They are enveloped by cortical reticular cells and consist of many closely packed cells with hairlike projections protruding from the taste pores (Figure 126) The nerve fibers leading to each taste bud, end in many nonmedullated arborizations which penetrate each taste cell

Many of the taste buds are not located directly on the surface of the tongue, but lie in depressions between elevations appearing as papillae on the surface. There are three types of papillae on the tongue: (1) The *fungiform* which has a general shape similar to a mushroom, (2) the *filiform*, and (3) the *circumvallate* papillae. The fungiform and circumvallate are found

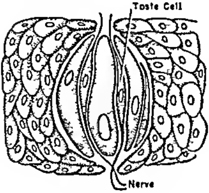

FIGURE 126

A taste bud from tongue papilla

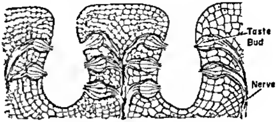

FIGURE 127

Diagram of a circumvallate papilla showing location of taste buds

chiefly on the posterior surface and contain a rather large number of taste buds (Figure 127). The filiform papillae lie on the anterior surface of the tongue and are probably concerned with tactile sensation. The nerves of the *chorda tympani* innervate the taste buds of the anterior two thirds of the tongue, those of the glossopharyngeal the posterior part and the root of the tongue, and those of the vagus the epiglottis, pharynx and larynx.

Taste acuity decreases with age as do the number of taste buds. It has been found that from infancy to about twenty years of age the average number of buds of certain papillae is about 245. In old age (seventy five to eighty years) these are decreased to an average of 88 buds, many of which are nonfunctional.

Classification of Taste

In spite of the fact that all taste buds appear to be similar morphologically there must be at least four different types since it is found that four distinct taste qualities exist. (1) The *sour taste* is aroused by acids or acid salts. The hydrogen ion concentration is the actual stimulus for this but its effect depends upon how well it can penetrate cells. For example, acetic acid is much more effective in producing a sensation of sourness than the same concentration of hydrochloric acid (a much stronger acid) because appar

ently, the former penetrates the cell much more rapidly. This taste is detected most readily on the sides or edges of the tongue (Figure 128). (2) The *sweet taste* is elicited by the presence of sugars (the alcohols, aldehydes, and ketones of the aliphatic series). Such substances as chloroform and lead acetate (sometimes called sugar of lead) also produce sweet sensations. The tip of the tongue possesses the taste buds most sensitive to the presence of sweet substances. (3) The *salty taste* seems to be caused chiefly by anions such as chlorides, bromides, iodides, sulfates and nitrates of sodium and potassium. The typical salt is, of course, sodium chloride. This taste is most evident on the tip and sides of the tongue. (4) The *bitter taste* is characteristic of alkaloids (quinine is typical and is used in the laboratory to demonstrate this sensation) and a series of unrelated substances, such as ether, Epsom salts, and picric acid. This taste is most concentrated at the back of the tongue and the pharynx.

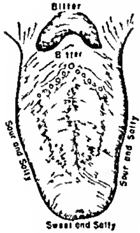

FIGURE 128

Surface of tongue showing papillae and location of various taste sensations

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16

Light Receptors

THE NATURE AND PHYSICAL PROPERTIES OF LIGHT THE SPECTRUM

Animals respond only to a very narrow band in the spectrum This is indicated in the accompanying figure (Figure 129) for vision in man Light waves are measured in angstral units The rays which affect the eyes of man are called visual rays and lie between 7500 angstroms (or 750 millimicrons) and about 4000 angstroms (or 400 millimicrons) Light, of wave

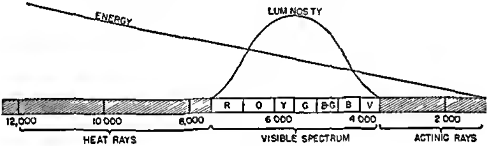


FIGURE 129

Diagram of the visible spectrum Greatest luminosity is in the yellow and green region the greatest energy in the infra red region

there is a change from yellow to green, at 5000 to blue green, at 4500 to blue, at 4000 to violet Beyond the violet, visibility ceases Thus, as the wave length varies over the spectrum there is a gradual change of color from red to violet

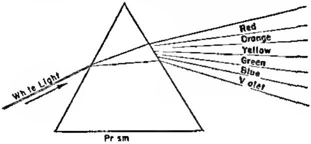


FIGURE 130

White light dispersed by a prism so that its constituent wave lengths are separated to form a spectrum

PROPERTIES OF LIGHT IMPORTANT TO VISION

There are certain properties of light which make it of utmost importance to vision These properties are (1) that of traveling in a straight line, (2) that of being refracted, and (3) that of producing a chemical change The first property, that of traveling in a straight line, is demonstrated by shadow formation This one direction is maintained as long as the light is passing through one medium, for example, air or water However, if light passes from air to water, or vice versa, it is refracted (bent) at the surfaces of the two media but, having been bent, will then continue again in a straight line in the new direction The principles involved in this phenomenon are shown in Figure 131 Most individuals, at some time or another have probably observed this second property of light when looking at an object in water A stick or pencil placed partly in water has the appearance of being

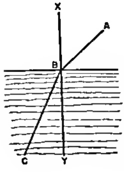


FIGURE 131

Diagram illustrating refraction of light The perpendicular ray (X–Y) does not change but any incident ray (A–B) is refracted the deflection is toward the perpendicular ABX the angle of incidence is always greater than the angle of refraction, CBY, and the greater the refractory power the smaller the angle of refraction The *index of refraction* is calculated by taking the ratio of the angle of incidence to the angle of refraction

bent It is this property that results in confusion when looking down into a body of water, especially at an angle, one is apt to judge that it is shallower or deeper than it really is

Light produces a chemical change in some substances This may be referred to as a photochemical change and is the third property of light mentioned above Photochemical changes are well demonstrated in the field of photography Before light may have an effect of this sort, it must be absorbed In other words, *light, in order that it may bring about a chemical reaction, must be absorbed (Draper's Law)*

THE OPTICAL PROPERTIES OF MATTER

It is common knowledge that one of the optical properties of matter is to absorb light to a highly variable degree Some matter, such as glass or water, appears to be almost completely transparent but when sufficiently thick it becomes apparent that these substances also absorb much light Light may be reflected, especially by matter which presents a smooth surface, so that many light waves are thrown off If, however, the surface is rough reflection takes place in all directions so that a diffuse light results due to the fact that the rays are scattered Therefore it is seen that four different processes may occur when light falls upon matter it may be (1) partially absorbed (2) transmitted, (3) reflected, or (4) scattered It is believed that in most cases all of these processes take place to a certain extent

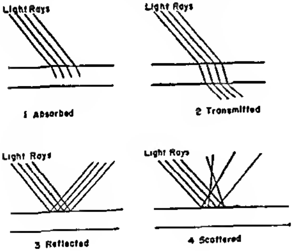


FIGURE 132

Illustrating the optical properties of matter

tem, which concentrates the light Lenses or lenslike structures are found in many types of photoreceptors It has been pointed out that even in plants, cells may be modified to function as lenses Lenses are found as well in the photoreceptors of many animals As in the case of all other stimuli discussed previously, protoplasm itself is sensitive to changes in light intensity This is evident in the case of an amoeba which, upon contact with light, moves away from the source The same can be said of sponges and coelenterates

Between the lowest invertebrates and the most advanced vertebrate animals there is a great difference in the structure of photoreceptors The simplest type is the red eyespot found in euglenoid forms of protozoans The eyespot (or stigma, as it is sometimes called) is sensitive only to light changes This is true also of those found in such groups as coelenterates and flatworms The colored pigment (red or black) absorbs light rays and the resulting chemical changes set off an energy flow which eventually brings about movement away from or toward the source of light

Figure 133 shows a green flagellate, indicating the position of the eyespot which consists of a lens and a pigment layer

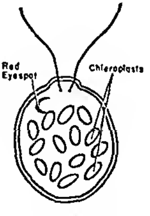


FIGURE 133

A green flagellate showing pigmented eyespot

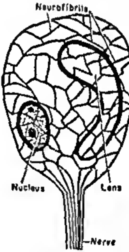


FIGURE 134

Single celled eye of an earthworm (after Hess)

There is apparently very little homology among the visual organs of metazoans Often the same animal will have two different kinds of eyes (insects) In the molluscans there are exhibited photoreceptors from the simplest eyespot to complex eyes somewhat similar to those of vertebrates

The earthworms and certain clams have eyes consisting of single cells having within them a lenslike structure, which refracts the light and concentrates it on a network of neurofibrils

A very simple eyespot is that found on the mantle edge of one of the mollusks (*Solen*) As shown in Figure 135, the eyespot consists of a group of light sensitive cells (epithelial cells), which have a heavy mass of black or

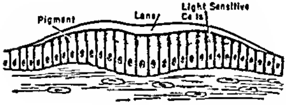


FIGURE 135

Section through the eyespot of a mollusk *Solen*

dark brown pigment at their distal ends, form a rather thickened region as a result of their lengthening The mollusks respond to light only when it strikes these spots The cuticle region also shows a transparent thickening which represents a lens, arranged so as to concentrate the light rays on the pigmented region

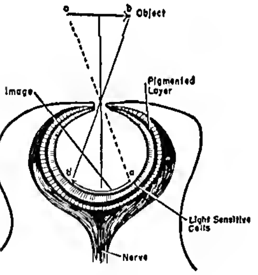


FIGURE 136

The pinhole camera eye of *Nautilus* (after Hess)

the cornea of more specialized photoreceptors Figure 137 shows a drawing of the eyespot of *Planaria* It consists of a pigmented cellular layer, in

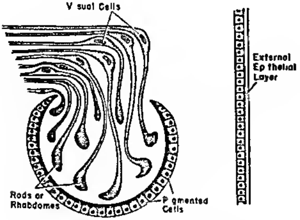


FIGURE 137

Section through the eyespot of a flatworm *Planaria*

the form of a cup and made up of more than one hundred separate cells The pigmented layer is in the distal part of each cell and the nucleus, in the proximal Many visual cells (rods or rhabdomes) are found, the so called afferent ends' of which come in close proximity to the pigmented layers of the cup These visual cells are specialized nerve cells the axons of which lead to centralized ganglia Note that their position in front of the pig ment layer is similar to the position of the end organs and nerve cells of the vertebrate retina

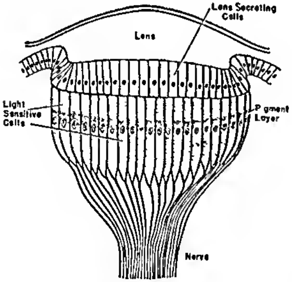


FIGURE 138

The simple eye of an insect

Anyone who has studied biology or zoology has some acquaintance with the very interesting eyes of the insects Some insects and the spiders have *simple* eyes (Figure 138) Other arthropods have compound eyes which

in some cases are supported by stalks so that they can be moved in different directions When examined closely with a magnifying glass these eyes are found to consist of a large number of squarelike or hexagonal partitions known as *facets* Each facet is the outermost part of an elongated structure called an *ommatidium* Each eye of a crayfish contains about 2500, and each eye of the dragonfly about 30 000 ommatidia Each ommatidium is separated from the others by walls lined with pigment cells and is able to receive impressions of only a small portion of the object directly in front of it Hence, a mosaic image of the object is reproduced in the eye by the separate impressions created within each of the many ommatidia For this reason it is thought that animals with compound eyes may see objects better if in movement since a series of changing impressions would result Thus the eye upon the movable stalk would be of a definite advantage Bees mosquitoes, and butterflies can distinguish color although not to the same extent as can humans

THE VERTEBRATE EYE

In vertebrates the visual mechanism consists of two eyeballs which in man and a few other animals are arranged in such a way that there is considerable duplication of image However, in most vertebrates the eyes duplicate only to a very slight degree Each eyeball is placed in the fore part of the bony orbital cavity and the range of vision is increased greatly by the fact that it can be moved in different directions by the muscles attached to it

The Extrinsic Muscles of the Eyeball

There are six external or extrinsic muscles attached to the eyeball which function in producing rotation of the latter four are recti and two are oblique muscles (Figure 139) One of the outstanding characteristics of eye move

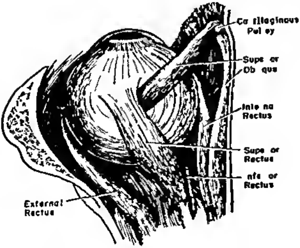


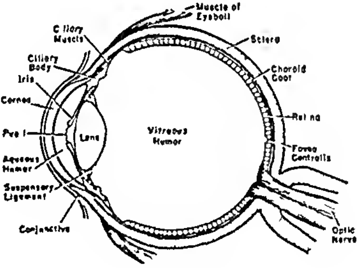
FIGURE 139

Left eyeball illustrating muscles

ments is the ability of these muscles of the two eyes to function in a coordinated manner If it were not for the fact that both eyes move at the same time in the same direction, there would very often be a doubling of vision

The Structure of the Eyeball

The eyeball is spheroid in shape and varies in size but is on the average about 24 mm in diameter It lies near the front of the orbital cavity, loosely embedded in fatty tissue and protected by the eyelids It is composed of three tunics or outer layers the outermost, the *tunica fibrosa*, the *tunica vasculosa* lying beneath it, and the delicate innermost retina or *tunica interna* The outer layer of the eye (*tunica fibrosa*) comprises two parts, the greater part of its external surface consists of *sclera* In fishes, amphibians, reptiles and birds, the sclera is partly or entirely made up of cartilage, in the whale and swordfish it is largely bone, in most mammals, it consists of densely interwoven bundles of white fibrous connective tissue accompanied by elastic fibers especially where the ocular muscles join the sclera



greater curvature than the rest of the eye. The cornea of different animals may vary greatly in size but, in general, nocturnal forms have larger corneas than diurnal, which, of course, gives the eye of the former type an advantage in that more of the weaker light rays may pass through it. The sclera is in contact with a very vascular, pigmented coat called the *choroid*. Anteriorly, the choroid becomes modified into several structures, namely the iris and the ciliary body which contains ciliary muscles and ciliary glands and to which the suspensory ligaments (discussed below) are attached. The choroid, ciliary body, and iris make up the *tunica vasculosa*, which is extremely vascular and is intimately bound or attached to the epithelial pigment layer of the retina. In cases where the retina becomes detached, its epithelial pigment layer remains adherent to the choroid. The *retina* (*tunica interna*) is spread out over the choroid layer and has connection with the optic nerve. All of these layers aid in the formation of the spherical cavity which makes up the internal part of the eye and which contains the *lens*, the *aqueous humor*, and the gelatinous *vitreous humor*. The lens, a biconvex structure with high refractive index, is found just behind the opening in the iris, being held in place by the *suspensory ligaments*. The aqueous humor is the fluid found in the chambers anterior to the lens of the eye whereas the vitreous humor fills the cavity behind the lens. These fluids, so called, are under pressure and the eye is, therefore, virtually a solid organ which possesses considerable rigidity.

foreign body with the eyelashes, (5) during sleep and other states of cerebral depression, (6) on sneezing

In many vertebrates (many fish, amphibians, and reptiles) the eye is covered with a transparent skin, and in others (sharks, crocodiles, and birds) a third lid or membrane moves transversely across the front of the eye with attachment at its inner angle. This structure is called the *nictitating membrane* and is present in mammals only as a rudimentary, useless structure in the inner corner of the eye. In fish, such a membrane protects the eye from sand and other particles in the water and at the same time does not shut out light entirely, so that the animal can still see objects. In the bird it protects the eye from particles in the air, prevents too much evaporation of tear fluid during flight, prevents, also, too much light from passing through to the retina, especially when the bird is flying toward the sun, and reduces the effect of ultraviolet and infrared rays which are more abundant at high altitudes.

The Lacrimal Glands

The cornea and conjunctiva are constantly moistened and washed by secretions from the lacrimal glands. The latter lie in the upper and outer part of the orbit and usually secrete just enough fluid for moistening the outer surfaces; the secretion keeps pace with evaporation. As the fluid leaves the glands it is spread over the eye by capillary attraction, aided especially by movement of the lids. If there is too rapid a secretion, some of the fluid can be carried away by the ***lacrimal canal*** located at the inner angle of

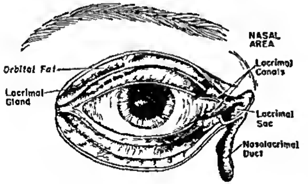


FIGURE 141

Right eye with upper and lower lids cut away to illustrate position of lacrimal glands, canals, and sac, and nasolacrimal duct

the eye. The *orifice*, or opening of the canal, is seen in the center of the papilla occurring there. The canal finally passes into the nasal cavity.

The secretion of tears is a reflex and is induced in many ways: (1) irritation of the cornea or conjunctiva, (2) irritation within the nasal cavity, (3) emotional excitement, (4) too brilliant an illumination. Secretory fibers are innervated by the seventh (facial) nerve.

Tear fluid is alkaline in reaction and consists chiefly of water (about 98 1 per cent) It also contains chloride and bicarbonate salts of sodium along with mucin, albumin, and debris It has a bactericidal action which is probably owing to lysozyme, an enzyme capable of destroying many types of microorganisms

The Corneo

The transparent cornea extends anteriorly from, and is a continuation of, the sclera It has the most refractive surface to be found in the eye, its radius is about 8 mm It is nourished by means of lymph which, in the healthy eye, can flow through the cell spaces When diseased, or during development, it may be nourished by blood vessels which proliferate in from its edge Within the cornea are found only bare nerve endings which undoubtedly account for the severe pain suffered when even minute foreign bodies come in contact with it

In general, the cornea functions in the same way as a photographic lens in that the light rays coming to it are refracted in such a manner as to focus slightly behind the retina The crystalline lens, immediately behind the iris permits a sharp focus The cornea may be compared to the coarse and the lens to the fine adjustment of a microscope

accommodation, because the pressure against the choroid would be so great that the action of the ciliary muscles would be ineffective.

Glaucoma

When pressures greater than normal develop in the eye, the condition is called "glaucoma." The normal pressure inside the eyeball (intraocular pressure) in man is about 25 mm Hg. It should be noted that the refractive properties of the eye would be unsatisfactory if the eyeball were not under tension. An unevenness in the cornea, or any abnormally relaxed ciliary body, would impair the usefulness of the eye as an optical structure. Thus, some degree of pressure within the intraocular fluid is essential. However, in certain abnormalities of the eye, the drainage canal may become closed. This may be owing to pressure on the lens in the farsighted eye or because of actual blockage of the canal with debris. Such abnormal pressures result in glaucoma. The signs of this condition are an extremely hard eyeball and dilated pupils which are very sluggish in action. Ultimately, injury to the retina may cause blindness.

The Iris

The iris situated in front of the lens (Figure 142) consists of a rather delicate framework or pattern of connective tissue, arranged for the most part

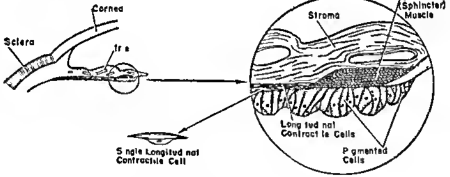


FIGURE 142

Section of the iris of the human eye, showing the arrangement of the sphincter muscles (for constriction) and the longitudinal contractile cells (for dilation). The latter are not true muscle cells.

in a radial fashion. It has a central opening called the "pupil" and contains two layers of smooth muscle fibers: the circular fibers, anteriorly arranged, which act as a sphincter to cause constriction of the pupil, and the radial fibers (posteriorly) which extend from the attachment of the iris at

the ciliary body to the rim of the pupil The radial fibers cause a dilation of the pupil when contracted The iris is normally opaque to light because of its pigmentation, the color varying greatly in different individuals The blue color of the eye is owing to posterior epithelial cells which contain a black pigment The iris appears blue because the color of the pigment is transmitted through the outer (anterior) stroma of the iris Other shades are a result of the presence of pigmented cells scattered through the stroma of the iris In the albino, pigmentation is almost entirely lacking and, therefore, most of the light that strikes the cornea will reach the retina unless the lids are closed For this reason the eye of an albino is extremely sensitive to light

The iris measures about 11 mm in diameter when viewed from the front, it is about 0 4 mm thick

Functions of the Iris

The iris functions in the same manner as the diaphragm of a camera It, therefore, can regulate the amount of light entering the eye, so that a more uniformly illuminated image may be reproduced on the retina, during accommodation to distant objects it allows more light to enter by dilation, whereas during accommodation to near objects it narrows so that less light enters the eye Much better refraction is obtained in the central part of the lens so that when the circular muscles of the iris are contracted, definition is improved considerably

The shape of the pupil, the central opening formed by the iris, varies in different animals Most animals have circular pupils but many nocturnal forms possess oval shaped, sometimes vertical pupils (for example, geckos, alligators, cats)

istration of many drugs such as atropine, homatropine, cocaine, and adrenalin, these drugs are called mydriatics (mydriasis is pupillary dilatation), (6) in hyperactivity of the adrenal glands, (7) during the excitement stage of anesthesia, and (8) in powerful stimulation of any sensory nerve

The Light Reflex

Constrictor fibers of the iris contract and dilators relax when light falls on the retina This is known as the "light reflex" An intense light might reduce the pupil to the size of a pin point The change from low to high illumination must be effected rather rapidly otherwise the pupil does not alter its size greatly The diameter of the pupil is greatest after it has been in darkness for some time (dark adapted), and may approach 7 5 to 8 mm In animals, such as man, having binocular vision and systems in which part of the fibers of the optic nerves cross over in the optic chiasma, the light reflex is bilateral Thus, when light falls on the retina of one eye it results in a simultaneous constriction of the pupils of both eyes

In some fish and amphibia, such as the eel and frog, the iris, itself, is sensitive to light and will contract when exposed even though the eye has been cut away from its connection, in fact a small piece of the iris shows contraction if exposed to light In other words, a nervous mechanism is not essential as in the case of mammals, contraction evidently being due to sensitivity of the pigmented muscle cells of the iris of these animals

Spherical Aberration

The changes in the iris resulting in constriction or dilatation of the pupil are important in, and act with, other structures as part of the accommodation mechanism In looking at near objects, the pupil must be small, otherwise the phenomenon known as *spherical aberration* is evident This, as shown in Figure 143, is because of the fact that the refraction of a lens differs some

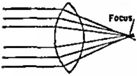


FIGURE 143

Spherical aberration The rays of light near the outer edges of the lens are refracted more so than those nearer the center

what in its different zones It refracts most perfectly at its center, which is why, in near vision, it is necessary to have all the lens, except the center covered with the iris Otherwise, the rays of light passing through the more peripheral parts are brought to a focus in front of the retina and a rather hazy image is produced thus when the pupil is dilated greater than normal clear

near vision is impossible When one glances at a distant object the pupil naturally dilates so as to allow as much reflected light from the object as possible to enter the retina Spherical aberration is not so evident when objects are viewed at a distance since the angles produced by the light rays coming from the objects are so small

Chromatic Aberration

The phenomenon of chromatic aberration may be explained in the following way If rays of white light are passed through a lens those rays which pass through its center do so as white light, whereas those that traverse the more peripheral parts of the lens are dispersed into their different color waves The lens functions in the same way as a prism and the image appears to be surrounded by colored circles

When light passes from one medium to another of greater density it is refracted because of the slower movement through the more dense medium All waves are not affected in the same way however thus the longer wave lengths (red) are refracted less than those at the violet end of the spectrum so that the violet rays are brought to a focus in front of the red rays (Figure 144) This is known as chromatic aberration and occurs in the lens of the eye if the latter is treated with atropine (or some other mydriatic) in order to dilate the pupil Under normal conditions the lens of the eye is covered

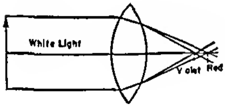


FIGURE 144

Chromatic aberration The rays of light near the outer edge of the lens separate into their colored components Consequently the red waves come to a focus behind the others

by the iris to such an extent that light rays do not strike near enough to its periphery to cause this phenomenon

In artificial lenses this condition can be overcome by the use of certain types of glass (combination of crown and flint glass) These are called achromatic lenses because refraction occurs without separation of the white light into the various wave lengths

Innervation of the Iris

Nerves from both divisions of the autonomic system send fibers to the iris The ciliary ganglion found just behind the eyeball acts as a relay station of the parasympathetic division and impulses passing over its postganglionic fibers cause contraction of the circular muscles and hence constriction of the

pupil Sympathetic postganglionic fibers from the superior cervical ganglia carry impulses resulting in contraction of the radial fibers and, therefore, dilation of the pupil

The Ciliary Body

The ciliary body and iris are continuations of the choroid coat (Figure 145) The ciliary body lies between the outer margin (*ora serrata*) of the

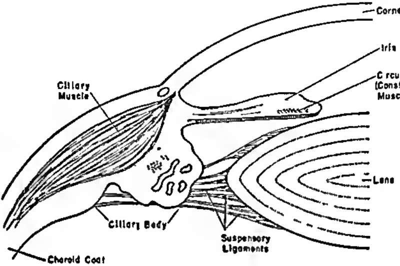


FIGURE 145

The structure of the anterior part of the eye showing the relationship of the ciliary body to the choroid coat, iris and lens

retina and the base of the iris It consists of ciliary muscles, glands, and ligaments The longitudinal ciliary muscles are shown in the figure, and, as indicated, are attached near the point where the transparent cornea and opaque sclera meet Thus, any contraction of these fibers exerts a pull on the choroid, tending to draw it forward Figure 146 shows the ciliary processes as seen from a point behind the location of the lens, which has been removed These are about seventy in number and are arranged in such a way as to form thickened areas around the margin of the iris Attached to the inner edges of the ciliary bodies are the suspensory ligaments which support the lens Naturally, any

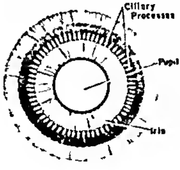


FIGURE 146

Iris and ciliary processes as seen from behind The lens has been removed

forward pull on the choroid releases tension on the ligaments which allows the lens to take on a smaller radius of curvature (or a greater convexity)

The Crystalline Lens

The crystalline lens is an elastic transparent biconvex structure which is made up of many concentric layers of fibrous cells and is enclosed in an elastic membrane or capsule

It is a refractory organ and its chief function is to bring the light rays already crudely focused by the cornea to a sharp focus on the retina One reason for its poor refractory power in the eye is that its index of refraction is nearly the same as that of aqueous humor and vitreous humor If the lens is dissected out of the eye and placed over printed matter it is capable of considerable magnification because its refractive index is greater than that of air If however the lens and newsprint are covered over with water there is very little magnification This approximates the condition existing in the eye and it is evident that the lens has relatively little focusing power

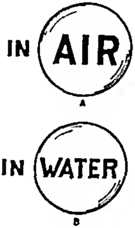


FIGURE 147

The relative magnifying powers of the crystalline lens of the human eye A in air B in water

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Pirenne M H *Vision and the Eye* (London Chapman and Hall 1948) ch 9 Vision in insects

Prosser C L *Comparative Animal Physiology* (Saunders 1950) ch 11 Vision in vertebrates and invertebrates

17

The Optical System of the Eye

THE OPTICAL SYSTEM of the eye consists of the cornea, aqueous humor, lens and vitreous body, they are concerned with focusing images of external objects on the retina of the eye This system is quite similar to the optical system of a photographic camera (Figure 148) The relative importance of the cornea and the crystalline lens in refraction has already been discussed However, refraction depends not only on density differences but also on the curvature of the lens Thus in Table 3 are given both radius and refractive index of the structures making up the optical system

TABLE 3

Refractive Structures and Indexes of the Eye

Radius of cornea	8 mm
Radius of lens anterior surface	10 mm
Radius of lens posterior surface	6 mm
Refractive index of cornea and vitreous	1.34
Refractive index of lens (equivalent)	1.42
Refractive index of aqueous humor	1.33

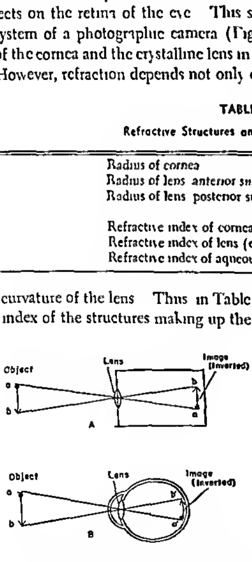


FIGURE 148

Comparison of the lens system of the eye B with that of a camera A

In Figure 148 the light rays from point *a* on the object, which strike the cornea (or the photographic lens), are refracted so that they converge at

a' on the retina (or the camera film) Those from point *b* bend so that they converge at *b'* In other words, the image is inverted, humans actually see the world upside down but interpret the sensation in the brain so that every thing is perceived right side up If one were to place a set of prisms in eye glasses so that the image on the retina would be right side up, he would see it as upside down

ACCOMMODATION IN LOWER ANIMALS

The mechanism for varying the focus of the eye is called the accommoda tion mechanism An eye which is focused on distant objects does not see near objects clearly and vice versa This is because the image of an object near at hand does not fall in focus upon the retina of the eye when the latter is adjusted for viewing distant objects Therefore, some mechanism is needed whereby the eye can change one or more of its structures in such a way as to focus on both near and distant objects as needed, in other words, the eye must be able to accommodate itself to these varying distances if it is to re ceive a clear cut, detailed image of surrounding objects The eyes of some animals lack this power altogether or are capable of accommodation only within narrow limits Frogs and alligators are chiefly dependent upon near vision and are not subjected to great variations in distances They are, *therefore, found to be lacking in ability to accommodate* Most inverte brates are chiefly 'shadow animals' in that it is not necessary for them to distinguish objects clearly, they respond to shadows This is especially true to animals below the arthropods and mollusks which possess no struc tures that would enable them to see detail

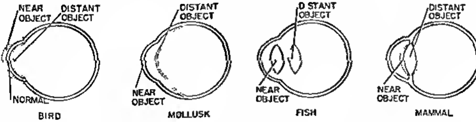


FIGURE 149

Methods of accommodation in different animals In the bird by increasing or decreasing the curvature of the cornea in some mollusks by contraction of muscles which pull the anterior part of the eye backward in fish by movement of the lens forward or backward by means of muscles attached to the lens in mammals by greater or lesser curvature of the lens

Actually, there are four possible ways in which an organ such as the eye can accommodate itself to near and far objects, and in nature are found

all of these possibilities represented by the eyes of certain animals: (1) In birds, the eyes are normally set for distant objects. The eyes of those birds which must swoop down on their prey from great heights, are capable of the exceptionally rapid accommodation necessary in order that the prey may be held in focus. Accommodation is accomplished by increasing or decreasing the curvature of the cornea (Figure 149). (2) Some mollusks have eyes in which muscles are found attached in such a manner as to pull the anterior part of the eye backward. In this way, the eyeball is shortened (the lens is brought nearer the retina) and the animal is able to accommodate for distant vision. (3) The eyes of fish do not possess ciliary processes and, hence, cannot accommodate by change in lens shape. There are special muscles *inside* the eyeball which actually pull the lens backward for distant vision (since the fish eye also is normally set for near vision). (4) In mammals, the lens changes shape. The contraction or relaxation of the ciliary muscles aid in this accommodation.

ACCOMMODATION IN MAMMALS AND MAN

The substance of the lens of the eye of mammals, including man, is elastic and is contained within the lens capsule. Without its normal attachments, the suspensory ligaments, it becomes strongly convex due to elasticity, so that its curvature is increased both anteriorly and posteriorly. It is much flatter when in proper position *within* the eye, its greatest radius of curvature being when the ciliary muscles are completely relaxed; that is, when the eye is focused on distant objects. A greater convexity or lesser radius of curvature is obtained upon contraction of the ciliary muscles. They pull the choroid coat forward, thus releasing tension on the suspensory ligaments which in turn allow the lens to decrease its radius of curvature (as it does when removed). When accommodated for distant vision the anterior part of the lens has an average radius of 10.0 mm.; for near vision, a radius of 6.0 mm.

Amplitude of Accommodation

The limit and amplitude of accommodation depends on several factors. The crystalline lens behaves like any other biconvex lens, and terms which apply to the latter also apply to the former. The *principal axis* is the line drawn perpendicular to and passing through the center of the lens. The axis usually traverses the *nodal point*, which corresponds to the optical center of the lens where parallel light rays pass through without refraction. Any other line that may traverse the center is called a *secondary axis*. When parallel rays of light pass through the lens they are refracted in such a manner

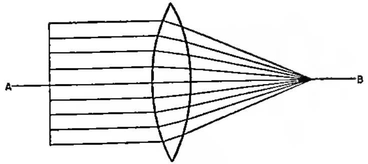


FIGURE 150

The refraction of parallel rays by a biconvex lens A–B, principal axis which passes through the center of the lens The rays nearest the edges of the lens are refracted more than the others The ray passing along the line of the principal axis is not refracted at all

as to pass through a definite point on the axis (Figure 151) This is called the *principal focus* and the distance between it and the center of the lens system, the *focal distance*

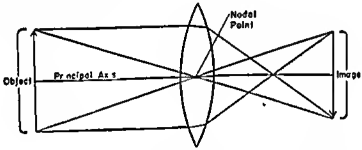


FIGURE 151

Image formation by means of a biconvex lens The nodal point is the very center of the lens system and rays passing through it are unrefracted

Often, in describing the function of the eye, the terms near point and far point are used The *near point* is the point nearest the eye and the *far point* is the most distant point from the eye at which an object can be seen clearly The latter is infinity in the normal person but usually is considered to be twenty feet, at which distance nearly parallel rays of light reach the eye from small objects The *power of a lens* is usually spoken of in reference to its principal focal distance in diopters (diopter being the unit of measurement commonly used) The unit of focal length is one meter and the *reciprocal of the focal length measured in meters is the power of the lens*

in *diopters*. Therefore, a lens with a focal length of 1 meter has a power of one diopter (1/1), and a lens with a focal length of ½ meter has a power of two diopters (2/1); conversely, if the focal length is 2 meters, the power of the lens is one half diopter (½).

It has been found that the power of the crystalline lens decreases as a person ages. In old age, there is hardly any ability to accommodate because of a loss of elasticity of the lens. This condition is called *presbyopia*. The power of the lens at different ages is shown in Table 4.

TABLE 4

Comparison of Age with Power of Crystalline Lens

Age in Years	*Accommodation in Diopters*
10	13.8
15	12.6
20	11.5
25	10.2
30	8.9
35	7.3
40	5.8
45	3.7
50	2.0
55	1.3
60	1.1

Young people have very elastic lenses and, therefore, can see over a rather wide range, being especially capable of focusing on near objects.

In summary, then, when the eye is accommodating for near objects, the ciliary muscles are contracted and, by pulling the choroid coat forward, release tension on the suspensory ligaments which allow the lens to present a more rounded (or curved) surface, which is the more normal condition of crystalline lenses. At the same time, the circular muscles of the iris contract to make the pupil smaller, which cuts down the amount of light entering the eye and prevents rays from entering too near the periphery of the lens where aberration may occur. In focusing on distant objects, just the reverse occurs, the lens is flattened and the pupil dilated. Sometimes the mechanism is so affected that accommodation is difficult or impossible. Thus, occasionally, after certain diseases, such as diphtheria or influenza, the ciliary muscles are paralyzed (probably due to bacterial toxins) but usually recover during convalescence. One of the first signs of glaucoma is failure to accommodate properly. This is owing to the effect of the great pressure of the aqueous humor and vitreous body on the lens, which prevents the

latter from changing shape Sometimes, because of eyestrain, spasms of the ciliary muscles disrupt the power of accommodation

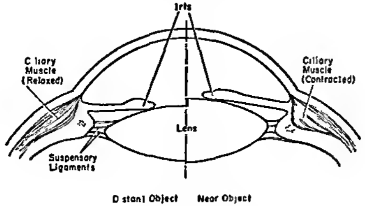


FIGURE 152

Changes in the eye during accommodation In near vision the ciliary muscles contract releasing tension on the lens which increases its curvature and the circular muscles of the iris contract making the pupil smaller

ABNORMAL REFRACTION IN THE EYE

Refraction, and the optical similarity between a camera and the eye, have been discussed already for the normal or *emmetropic* eye It is clear that the eye, at rest, is so constructed that when light passes through the cornea the aqueous humor, lens and vitreous body, it is bent or refracted in such a way that it is focused on the retina But if one should concentrate his vision upon an object at a greater or lesser distance, then the image is not quite in focus The mechanism for accommodation takes over automatically and by the action of the ciliary muscles, the lens either takes on a lesser radius of curvature (that is, becomes more convex) or is flattened out

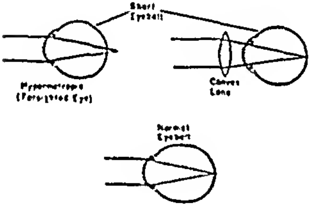
There are many cases however, in which the curvature of the cornea is so extreme that the focus lies too far in front of or too far behind the retina The ciliary muscles may be unable to accommodate under these circumstances

FARSIGHTEDNESS (HYPERMETROPIA OR HYPEROPIA)

In the condition occurring in farsightedness a person cannot see distinctly t relatively short distances The image is focused behind the retina to ich an extent that the ciliary muscles (or processes) cannot relax sufficiently he suspensory ligaments, therefore, do not subject the lens to sufficient ension to flatten it and so allow for proper focus Farsightedness is chiefly

the result of one of two conditions: (1) the eyeball is too short for the lens system, the most common cause, or (2) the eyeball may be the proper length, but the lens power is below normal. Infants have farsighted eyes, being born with the eyeball too small for the lens system. As the infant grows into childhood, the eyeball grows more rapidly than the lens system until finally the former reaches a normal size at which time it usually stops growing. In some cases, the eyeball for one reason or another never does reach normal size and the eye remains farsighted. This is an example of the first type.

The second variety is found in the eyes of older people. As one ages, the lens of the eye becomes more and more solid and loses its elasticity. Since the eye and its appendages are constructed in such a way that it is focused for distance when the ciliary muscles are relaxed, the lens is flattened and tends to harden (presbyopia). In both types the focus is behind the retina.



ing the pressure, the eyeball becomes stone hard (*glaucoma*). The constant attempt to accommodate for near vision may also result in pulling the eyeball inward (strabismus); this condition may become permanent. Eyestrain is also caused by too frequent attempts at accommodation; the strain is on both ciliary and the external muscles of the eye. Headache and fatigue are associated with it.

As shown in Figure 153, treatment of farsightedness involves the use of suitable convex lenses. They aid the cornea (and lens) in bending the light rays more sharply.

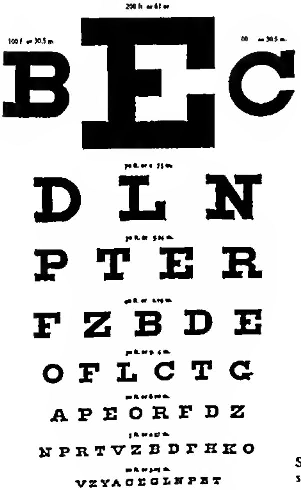


FIGURE 154

Snellen's chart for testing nearsighted and farsighted eyes

NEARSIGHTEDNESS OR MYOPIA

The abnormality nearsightedness is just the opposite of farsightedness and the person suffering from it is unable to see distant objects distinctly

The light rays come to a focus in front of the retina—so much so, that the mechanism for accommodation cannot carry out its function properly. There are two conditions that result in nearsightedness (1) the eyeball is too long, or (2) the refractory power of the lens is too great. It is chiefly because of the former.

As stated previously, the eyeball usually stops growing when it reaches normal size. Often, however, when the eye is used too frequently in early childhood for close work, the eyeball may continue to grow until it finally reaches a size too great for the lens system. Such a condition becomes worse if steps are not taken immediately to correct it. Correction is carried out by prohibiting the child from carrying on close work such as reading fine print or doing fine embroidery, and by the use of concave lenses (Figure 153) until growth of the eyeball ceases and the remaining structures within have had a chance to catch up. Myopia or hypermetropia may be detected by using Snellen's test charts with which most persons are familiar (Figure 154). The numbers above each letter indicate the distance at which the normal eye should be able to identify the designated letters (on the chart of the original size). If, for example, an individual could read the same letter at 20 ft (which is the average distance for the individual with normal eyesight), as can the normal average individual, his vision would be reported as 20/20 (normal). If he reads letters at 10 ft which the normal eye can read at 20 ft, the ratio is 10/20, and the test shows that the individual is near sighted. In hypermetropia the fraction would be reversed.

ASTIGMATISM

The condition known as astigmatism is present in all eyes to a certain degree but is detectable only if it becomes extreme. It is usually caused by a difference in the vertical and horizontal curvatures of the cornea. Generally the lens also has a difference in curvatures which being opposite to that of the cornea partially counteracts the effect of the latter. Occasionally, however, the differences in corneal curvatures are too great, and as a result the light rays will come to a focus in different planes and certain parts of an object may be clearer than others. Astigmatism may be caused also by abnormalities in lens curvature, but this occurs very infrequently. Astigmatism may be detected by use of charts such as that shown in Figure 155. In astigmatism, if the eye is accommodated for the vertical lines, the horizontal lines are indistinct or vice versa.

In correcting astigmatism, lenses with the same curvatures as the cornea are made but they are held, when in use, so that the greater curvature of the

lens will correspond to the lesser curvature of the cornea, and the lesser curvature of the lens, to the greater curvature of the cornea

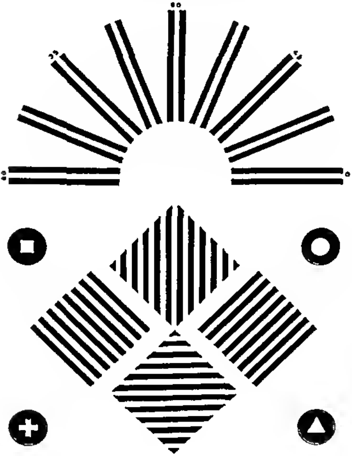


FIGURE 155

Chart used to detect astigmatism If the lines on one side appear to be indistinct when the eye is focused on the lines of the other side the eye is said to show astigmatism

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Davson H *The Physiology of the Eye* (Blakiston 1949) pp 320–435 Optics of vision

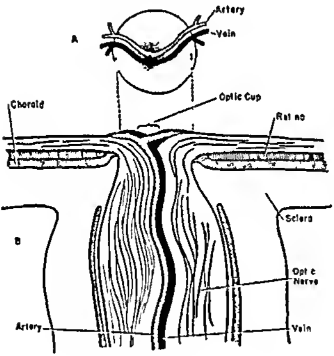
Southall J P C *An Introduction to Physiological Optics* (New York Oxford University Press 1937) chs 2 3 Optics of the eye

18

The Retina

MICROSCOPIC STRUCTURE OF THE RETINA

THE RETINA is a membrane-like structure that lies between the choroid coat and vitreous body and extends forward almost to the posterior part of the ciliary body. It is thinner in front than in back, ranging from 0.1 mm. near the ciliary body to 0.4 mm. posteriorly.



of center in the case of the left eye. It passes through the sclerotic and choroid coats and the posterior part of the retina from where its neurons spread out all over the retina; in the fovea, however, there is an almost total absence of nerve fibers and cell bodies. The area surrounding the optic nerve as it enters the retina is referred to as the *optic disc* and is about 1.8 mm. in diameter. At the center of the optic nerve is a small depression sometimes called the *optic cup* through which the blood vessels of the retina make their entrance and exit. These vessels nourish and carry away waste materials from the cells of the retina, and are quite separate from the vessels that feed the choroid and sclerotic area. Immediate and permanent blindness follows if they are damaged, although the choroid vessels may be intact. There are no end organs in the disc, hence, it is insensitive to light and is called the *blind spot*. This can be demonstrated by means of Figure 157.

FIGURE 157

Cross and circle diagram for demonstrating the presence of a blind spot in the retina. *With the left eye closed, hold* the book about 18 inches from the right eye which is fixed on the cross. If the book is now brought closer to the eye, a position is reached (approximately 10 in. from the eye) where the circle disappears; it is focused on the optic disc where there are no visual end organs and hence it can not be seen. If the figure is now moved in either direction the black spot can be seen again.

Microscopically, the nervous part of the retina is composed of several layers of different types of neurons and receptor cells. As shown in Figure 158, these are (1) a layer of pigment cells, in close contact with the choroid coat, (2) a layer of rods and cones, the functional units of the retina, (3) a layer of bipolar nerve cells, (4) a ganglion cell layer, and (5) a nerve fiber layer.

The layer next to the pigmented cells consists of rods and cones. The rods are cylindrical in shape and about 60 microns (0.06 mm.) long by 2 microns in diameter. The cones are much shorter (35 microns) but thicker (6 microns). There are about seven million cones in the human eye, and the rods have been estimated to number anywhere from seventy-five to one

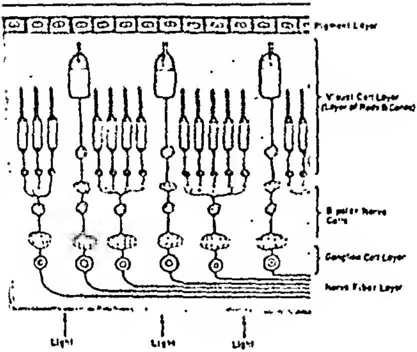


FIGURE 158

Diagram of section through retina showing its microscopic structure. Arrows indicate direction of light.

hundred and seventy million. Each cone cell in the central portion of the retina has a separate pathway to the visual area of the occipital lobe whereas many rods may make synapse with a single neuron. Near the periphery, however, ten cones and as many as two hundred and fifty rods may make synapse with a single neuron.

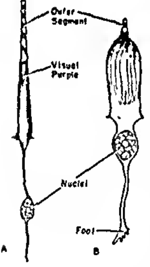


FIGURE 159

Sketch of a rod, A, and a cone, B, from the human retina.

The cones are found most densely packed in the *fovea centralis*. There are about thirty-four thousand cones in this area alone. Actually, they are so closely packed, that when a cross section is made of the region, it presents the appearance of a honeycomb, the pressure against each cell causing a hexagonal shape. The great number of cones in this area undoubtedly explains the visual acuity of the fovea. *Rods are present, mixed with cones in* the region immediately surrounding the fovea. It is found that the proportion of cones decreases as the periphery of the retina is approached, and

that they are absent entirely at the periphery The reverse is true of the rods

The fovea, then, is peculiar in several ways (1) it contains cones only, which are longer and more closely packed than elsewhere, (2) the rows of nerve cells and fibers are pushed to one side so that the rays of light contact the cones directly instead of first passing through other cell masses, thus, the fovea appears hollow, (3) it is devoid of blood vessels, (4) visual purple (the pigment found in rods) is absent, which can be explained by the absence of rods

The fovea is a late development in the eyes of mammals, it becomes more and more pronounced from lower mammals to man Not only is distinctness of vision greatest in the fovea but also appreciation of color, which is lacking at the periphery of the retina This indicates that one of the functions of the cones *is perception of color, since cones predominate in* the fovea and are lacking at the periphery

EXPOSURE OF RETINA TO LIGHT

When light reaches the retina, several changes are evident (1) There is an electrical change in that an action potential is produced upon stimulation (2) Chemical changes also occur and are of two types the retina becomes more acid in reaction, and the two pigments (visual purple in rods and fucsin in pigment cells) become bleached Visual purple (rhodopsin) is bleached most readily by light in the middle of the spectrum (3) In some animals, such as the frog or fish certain structural changes occur when

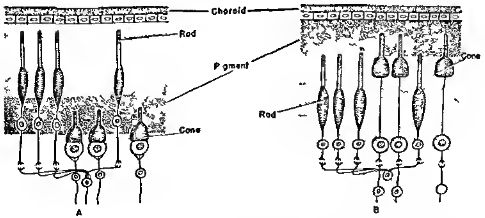


FIGURE 160

Mechanical changes in retina during light and dark adaptation A light adapted retina showing expansion of pigment and retraction of cones B dark adapted retina with cones extended to rods which are slightly retracted the pigment has migrated to a posterior position

light strikes the retina The cones shorten as they are drawn toward the inner surface of the retina by means of a highly contractile stalk called the myoid', the rods remain the same length At the same time, the pigment from the outer layer of the retina moves upward, thus giving better protection to the rods against excessive stimulation by the light On the other hand, in the dark adapted eye (such as one that has been exposed to darkness for a few minutes) the condition is reversed, the rods are drawn upward by their myoid, but the cones are lengthened and the retinal pigment has moved again to the outer retinal region Attempts to demonstrate similar mechanisms in the mammalian eye have not been convincing It is thought that such photomechanical changes in these lower animal forms may act as a substitute for the pupillary reactions which occur in mammals (4) Physiological changes also are evident in that the dark adapted eye is color blind and the light adapted eye is useless in dim illumination

NIGHT BLINDNESS

One of the oldest known diseases of man is night blindness—a failure to see objects in dim light—which has afflicted large populations throughout history It occurred in ancient Egypt (1850 B C, and before) where the proper diet for its treatment was actually known, liver in various forms was usually prescribed These ancient people, of course, did not know that vitamin A which is stored in the liver of animals, was the reason for the curative effects In fact, many unpleasant prescriptions were suggested for treatment and great emphasis was placed upon the necessity of that part which made it unpleasant During the nineteenth century the use of liver oils in the treatment was recognized but it was not until 1917 that the effective ingredient of liver oils was found to be vitamin A, an essential constituent of visual purple

PHOTOCHEMISTRY OF THE RETINA

Visual purple (rhodopsin) is highly concentrated in the retina and is found only in the rods Colored substances are found, but in very minute concentrations, in the cones also The retina, therefore, when dark adapted has a purplish or violet tinge which soon fades to a yellowish color when exposed to light

Visual purple has a relatively large molecule (molecular weight about 270 000) consisting of a large protein molecule connected with ten smaller, colored molecules called *chromophore groups* When light strikes visual purple the latter is broken down to a yellowish compound, *retinene*, and a protein In darkness the two reunite to form visual purple Such a process

is seen in terrestrial vertebrates and in marine fishes In fresh water fishes a very similar process occurs, except that a slightly different form of vitamin A (called 'vitamin A_2,' as contrasted with the usual vitamin A_1) goes into the structure of a material, ***porphyropsin***, which is broken down by light as is rhodopsin

Since vitamin A is found in the visual purple molecule, absence of this vitamin in the diet ultimately means lack of visual purple formation, thus, so-called "night blindness" occurs because visual purple cannot be synthesized It is evident, now that the rods function in dim illumination and that this function is possible because of the presence of visual purple which can absorb the extremely weak light rays

ROD VISION

The rods synthesize visual purple in darkness, a process known as dark adaptation The absorption of small quantities of light by visual purple brings about a chemical reaction (rhodopsin $\longrightarrow$ retinene) and the energy released causes an impulse to flow from the rods over the nerves leading to the cerebrum

The longer one remains in darkness or dim illumination, the greater the quantity of visual purple produced (up to a point of saturation) and, therefore, the greater the ability to absorb light Most humans have experienced the results of such phenomena For example, when one enters a theater during midafternoon after exposure to brilliant sunlight, he can barely see although some light is reflected from the screen The sunlight prevents synthesis of visual purple, in fact, its action totally decomposes it Hence, when one enters the theater, there is no pigment within the rods of the retina that will absorb the dim light and produce energy for stimulation After a few minutes in darkness, however, enough visual purple is synthesized to take care of the dim illumination—with the result that one can see readily The reverse process occurs when one leaves a theater (with eyes completely dark adapted) and is exposed to brilliant sunlight The visual purple is broken down so rapidly and the intensity of stimulation is, therefore, so great that much discomfort is felt After a few minutes, the glare disappears and the eye is again light adapted

It is known from the experience of most individuals that one finds it very difficult to match or even to perceive colors in dim illumination Certainly if the visual purple had any connection with color vision, colors would be perceived best by the dark adapted eye Evidently the rods function only in dim illumination This may be demonstrated further in the early evening hours when the first stars make their appearance They are most

readily seen if the light rays reflected from them strike the periphery of the retina which contains chiefly rods When the gaze is directed toward a star and its dim rays strike the fovea, it seems to disappear The fovea contains no rods or visual purple and, therefore, these light rays are not absorbed in this area

FUNCTIONS OF OTHER EYE PIGMENTS

Attention has already been drawn to the pigmented cells of the iris When light strikes the iris it does not cause any chemical reaction so far as is known The pigmentation functions only in preventing too much light from entering the eye

Another pigmented area is found in the outer layer of cells of the retina This coloring matter is *fuscin*, also functioning in absorption of light rays, that is, the rays which pass through the retina to the rods and cones If it were not for this absorption, much light would be reflected and scattered over the retina so that a clear image would be almost impossible Fuscin, itself, is present in these pigment cells in the form of plates, needles or prisms Strong light bleaches it but the breakdown processes or products apparently have no visual function

CONE VISION (COLOR VISION)

The existence of pigmented substances in cones was not known until recently, rhodopsin (of rods), on the other hand, has been known for over seventy years The cones are sensitive to bright illumination and also function in color vision Color vision is based upon three primary colors—red green, and violet—and it is thought that the cones contain three different photopigments for absorbing the three types of primary colors respectively In chickens and other birds, as well as amphibians and reptiles, the cones actually contain three types of differently colored oil globules (cone oil) red, golden and greenish yellow These may be comparable to the three filter systems in use in color photography No colored globules or other structures have been found in the retina of man but undoubtedly there are substances present which are capable of selective absorption It is generally believed that color vision is poorly developed or entirely absent in most lower animals This is true of most invertebrates, however, it is found that bees mosquitoes and butterflies (representatives of three different types of insects) can distinguish color although they do not have the range of color vision possessed by man Among the vertebrates color vision is found in many fish reptiles, diurnal birds, and comparatively few mammals Nocturnal birds and nocturnal mammals do not possess color vision and even

many diurnal mammals are without it. The bull, which supposedly is infuriated by the color red, is color blind and would respond to any other color just as well. There is no evidence whatever that dogs or cats can see color, the same is true of the horse. The primates, for the most part, have very excellent color sense.

COLOR SENSATION

Perception or sensation of different colors is not equally distributed over the retina. This can be ascertained by means of a *perimeter* which is an instrument used for mapping the visual field (Figure 161). With it, one finds

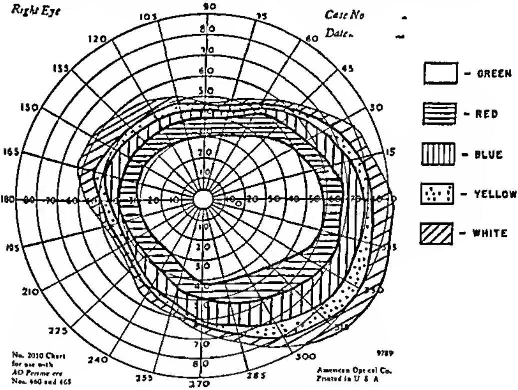


FIGURE 161

on a surface and although physically it is the total absence of light or color, in consciousness it is a definite sensation just as is red, blue, or any other color. It is a sensation produced, however, by the absence of stimulation.

Complementory Colors

The sensation of white is felt not only by mixing all of the colors as just described but also by combinations of the so-called "complementary colors"; that is, red and blue-green rays, or violet and yellow rays, or blue and orange, if these combinations act simultaneously or in rapid succession on the same part of the retina. Two such colors thus producing the sensation of white are said to be complementary to one another. In the laboratory a rotary apparatus or color wheel is used, consisting of a flat disc equipped so that different colored paper can be arranged in desired combinations. The rapid turning of the wheel will "fuse" the colors and, if they are complementary, the result is a sensation of white.

Attributes of Color

Three attributes of color are recognized: (1) *Brilliance* (brightness, or luminosity) which varies over the spectrum and depends upon intensity of stimulation. At the extreme red and violet ends of the spectrum there is less brilliancy than there is between them. It is said that the human fovea can recognize six to seven hundred different degrees in brightness. However, although one can tell which of two red colors or two green colors is the brighter, it is almost impossible to arrange different colors according to their brightness, that is, it is difficult often to judge whether a particular green color, for example, is brighter than a red. Discomfort is felt if the brightness is too intense; this is known as "glare." (2) *Hue* is the characteristic or attribute of certain colors which enables one to classify them as reddish, yellowish, bluish, and so forth, and is determined by wave length. (3) *Saturation*, another attribute, is a mixture of the particular color in question with white light. A completely saturated color is one which is entirely free of white light. This, then, would refer to the "purity" of the color.

THEORIES OF COLOR VISION

Many theories (eighty or more) have been advanced in an attempt to explain color vision but none of them are wholly satisfactory. Practically all of them assume the presence of three photosensitive substances in the cones. The *Young-Helmholtz Theory* seems to be the most acceptable to physiologists, although it fails in many respects to explain color vision fully. It assumes the presence of three types of cones: in one group there would be

a red absorbing substance, in another group, a green absorbing substance and in still another group of cones, a violet absorbing substance When waves of red light (that is, long waves) reach the retina they are absorbed by the red absorbing substance, and an impulse is initiated over the neurons leading from these cones to an area of the occipital cortex In the same way violet is seen if the short waves are absorbed or green if intermediate waves are absorbed For the most part, it is found that mixtures of these *fundamental* colors are more prevalent in nature than the single colors The sensation of yellow is produced when the cones are stimulated by both red and green waves since both red absorbing and green absorbing cones are affected In the same manner, the sensation of blue results when both green and violet absorbing cones are stimulated

White light would be perceived if all three were affected at once This theory assumes the validity of Muller s Doctrine of specific nerve energies

The process by means of which these different colors are perceived by the occipital cortex is not understood One can be fooled by color sensations just as by sensations concerned with other receptors For example in binocular vision, fusion of two primary colors produces a sensation of a third color If a red filter is placed in front of one eye and a green one in front of the other, a sensation of yellow is experienced This sensation is produced in the cortex and certainly is aided by the fact that part of the fibers of each optic nerve cross over and mix with fibers of the other before terminating in the cortex

COLOR BLINDNESS

The condition of color blindness exists when light which enters the eye and strikes the end organs in the retina, fails to evoke the usual color sensations It is claimed that about 4 per cent of men and about 0.4 per cent of women are color blind

John Dalton (1774) was the first to record and accurately describe color blindness Dalton himself, was evidently red green blind since he could not tell the difference in color between two objects if one were green and the other red

The red blind person confuses red with green and any color mixture containing red is seen as though no red were present Thus, the color purple, which is a mixture of red and blue appears blue, orange appears yellow

Color blindness is inherited and the mechanism involved is similar to that of hemophilia (page 325), that is the female is usually only the carrier, whereas the condition appears in the male Females inherit color blindness only if the genes for color perception are absent in both parents

There are seven possible types of color blindness according to the Young Helmholtz theory, and all types are known to occur although violet blindness is very uncommon They are, in the order of their frequency of appearance in humans (1) red green blindness, (2) red violet blindness (3) red blindness (4) green blindness (5) green violet blindness (6) red green violet blindness and (7) violet blindness Total color blindness is called monochromatic or achromatic vision and is extremely rare In one afflicted with total color blindness all vision is similar to normal twilight vision in that all objects appear to be black, gray, or white

Testing for Color Blindness

Color vision may be tested by several different methods Two of these are most common (1) Pseudoisochromatic diagrams have been devised by Ishihara This test consists of several cards on which colored spots of various sizes are printed A figure or letter also made with spots is superimposed on the field The coloring of the spots is blended in such a manner that in one case only a normal eye can detect the figure while in another, only the color blind eye can distinguish it (2) The Holmgren matching tests, in which pieces of yarn of various colors and hues are matched with standards The color blind person is unable to match these properly

CONTRAST EFFECTS

There are many examples of phenomena involving the effects of contrasting colors It is the common experience of everyone that if a white piece of paper is placed on a black background the paper appears whiter by contrast than otherwise The same applies to a black paper on a white background the former appears blacker If the paper is colored for example, green and placed against a white background it appears to be more saturated Also if a blue paper is placed against a yellow background it appears bluer (or vice versa)

These phenomena are examples of *simultaneous contrast* Other phenomena result in *successive contrast* which consists of the appearance of a complementary color after one focuses his eyes upon a colored surface for a minute or so and then shifts his vision to a gray surface

AFTEREFFECTS

The aftereffects described below are common and well known experiences If one stares at the flame of a candle or at an electric light for 30 sec or more and then the eyelids are closed or the gaze shifted to a dark background the flame or light can still be seen (persistence of vision) in its

natural color and then gradually fades This is a *positive afterimage*

Negative afterimages are produced by gazing at a white background after stimulating the eye with a light or other object A white object then appears dark and the image of a colored object has the complementary color For example, if one stares at a blue green object and then looks at a white surface, he sees the image as red, the complementary color

PERSISTENCE OF VISION

When the retina is stimulated by a short flash of light, it is well known that the sensation of light remains for some time after the stimulus is removed This phenomenon is known as persistence of vision and is the basis of cinematography In moving pictures, there is an interval between one frame and the next Whether or not the dark interval is noted by the eye depends upon the frequency at which the light frames are flashed on the screen That is, if they appear rapidly enough so that the sensation of the one lasts over until the next frame appears, the dark intervals are not noticed and the lighted frame appears as one If the frames do not appear rapidly enough, a ' flicker is noticed

Fusion occurs when sixteen or more frames per second are flashed on the screen The peripheral area of the retina is more sensitive to the dark intervals than the central portion A flicker, therefore, is especially noticeable in silent pictures if the head is turned so that the light falls upon one side of the retina Persistence of images may be due to chemical stimulation that continues momentarily after the stimulus is removed

BINOCULAR VISION

The eyes of man are arranged so that when he fixes his gaze upon an object, each eye receives slightly dissimilar images thus, he is said to have

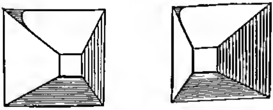
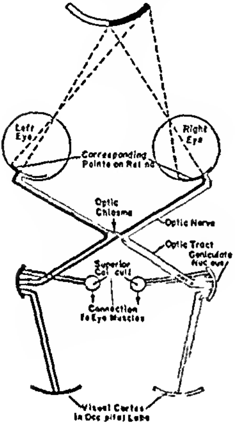


FIGURE 162

Illustrating stereoscopic vision with two pyramids the one at the left as seen with the left eye that at the right as seen with the right eye

binocular vision This is demonstrated by looking at an object, first with one eye and then the other The right eye sees a little more of the right side of the object and the left eye a little more of the left side of the object (Figure 162) The points of the retinae which receive identical (or almost identical) images are called *corresponding points* However the corresponding

points are in different portions of each retina (Figure 163); that is, the rays of light that form an image on the temporal half of the right retina form the same image on the nasal half of the left retina, and vice versa. Nerve pathways from these points on each retina pass through the optic



and left sides This is a probable explanation of the fine coordination in eye movements, that is, impulses from each side of the cerebrum are transmitted to each group of muscles If the muscles are not working in coordination, there results a condition of *divergent strabismus*, in which both eyes turn outward when only one is voluntarily moved outward, or of *convergent* (internal) *strabismus* or crossed eyes in which the eyes turn inward Under these circumstances the images in the two eyes do not fall upon corresponding retinal points and *double vision or diplopia* results There appear to be two objects, one overlapping the other

ADDITIONAL READING

Hartridge H , *Recent Advances in the Physiology of Vision* (Blakiston, 1950) ch 8 Light and color

Linksz A , *Physiology of the Eye, II Vision* (New York Grune and Stratton, 1952), chs 4–8 Color and color vision

Pirenne, M H , *Vision and the Eye* (London Chapman and Hall, 1948) Retinal functions in general

19

The Ear

SOUND RECEPTION

Sound Receptors in Invertebrates

EXCEPT FOR the insects, specialized sound receptors are not found in the invertebrates, although most of the latter respond to vibrations of some kind. The earthworm, for example, can detect ground vibrations caused by stepping movements. Some insects emit definite sounds, and, therefore,

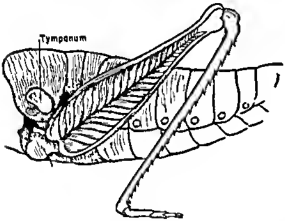


FIGURE 164

The abdomen of a grasshopper showing the tympanum or "ear" on the first abdominal segment.

one might expect them to have fairly well-developed organs for the reception of sound. Grasshoppers and locusts have such organs which consist of a membrane (tympanum), covering numerous sense cells; these are located on the sides of the abdomen just above the base of the third pair of legs. Grasshoppers will respond to artificial notes in the same range of sound as those produced by other grasshoppers. They seem to be capable of hearing notes between 430 to 28,000 cycles per second. Similar structures are found on the abdomens of cicadas and the thorax of moths.

Development of Sound Receptors in Vertebrates

In the lowest classes of vertebrates the ears are poorly developed. Fishes have no cochlea (the structure in humans containing the sense organs for hearing) but do have end organs (maculae) in the sacculus which seem to act as auditory organs. Many investigations have been made on hearing in

fishes, for at one time it was doubted by many that these animals could hear Although it is true that many fishes appear to be deaf, some can be taught to respond to definite notes The marine fishes respond only to notes of low frequency, fresh water species are sensitive to frequencies of several thousand cycles per second The lateral line organs of fish are thought by some to respond to sound, this is quite true if the sound is within a certain range The cells of the lateral line organs are also sensitive to touch, pressure and vibration (even frequencies of about 6 cycles per second) The fish is thus able to avoid rocks and other fish as a result of pressure stimuli reaching this organ

Frogs, and other amphibia, have poorly developed cochleas, but they respond to tones of frequencies ranging from 50 to 10,000 cycles per second Reptiles have a well developed but small cochlea In snakes this organ is better developed than in amphibians, but the former have no tympanum They cannot hear air borne sounds but they do respond to vibrations coming from the ground through the skull to the end organs

The cochleas of birds are not quite so well developed as those of mammals It is obvious, however, from their ability to imitate that they must hear very well

Sense of Hearing in Mammals

The ear of mammals is made up of structures that serve two general senses (1) hearing and (2) proprioception (equilibrium) Since, however, that part concerned with reception of sound is perhaps better known to most of us, it will be discussed first

The end organs of the innermost part of the ear are actually modified forms of tactile tissue The ears of mammals are so constituted that their functions consist of (1) collecting and intensifying sound waves, and (2) conveying them to the auditory end organs which are found deeply embedded within the skull

SOUNDS AND THEIR SOURCES

Physically, sounds are vibrations from various sources which reach the ears as alternating *rarefactions* and *condensations* of the air, exemplified by the vibrations of a tuning fork prong

Everyone has observed that sound travels considerably slower than light A locomotive, at a considerable distance, is seen to discharge steam from its whistle long before the sound reaches the ear Altitude (because of the rarity of air), temperature, and the character of the medium affect the speed of sound, but usually it is approximately 340 meters per second It is more

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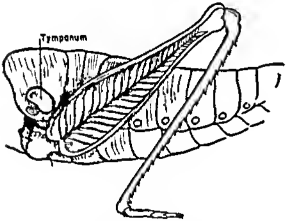

FIGURE 164

The abdomen of a grasshopper showing the tympanum or ear on the first abdominal segment

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rapid in water (1450 meters per second) and still more rapid in wood (about 13,000 meters per second)

Sound waves are sometimes reflected, and these reflections are known as echoes

Sounds may be classified into two groups—*notes* and *noises* A *note* is produced when the waves reach the ear periodically or uniformly, a *noise*, when they are aperiodic It is not always easy to distinguish between them

The sources of sounds are quite varied, but the fundamental property of a source that results in the sound is the same in all, that is, the ability to vibrate within certain limits For example, a book closed suddenly with a snap produces sound, whereas one closed slowly does not

There are certain properties by means of which sounds can be distinguished (1) *Pitch*, or *tone*, depends upon the length of the sound waves, or, in other words, the number of waves reaching the ear in unit time The greater the number (or the shorter the waves) the higher the pitch The range for the human ear on the average is between 40 and 20,000 vibrations per second A dog can detect much higher frequencies Thus, special whistles can be made of such a high pitch for dogs that it is not detected by the human ear It is said that they can hear pitch of about 35,000 vibrations per second Bats are even more sensitive to sound, their limit said to be about 100 000 vibrations per second (2) *Intensity* or *loudness* is that property which depends upon the force of the vibrations The harder a tuning fork prong is struck, the more intense will be the sound (3) *Quality* or *timbre* is produced by the mixture of tones and overtones in a vibrating body This is the means by which the same note struck upon different instruments can be distinguished If a single note is struck on a piano, or played on a violin, the pitch will be the same, since the number of vibrations of the string is the same in both cases However, in each of the different strings there will be separate vibrations within its parts, so that two, three or four portions will have their own vibrations which are independent of those of the whole string Thus, the ear will be stimulated not only by the fundamental vibrations (determining pitch), but also by the separate vibrations of the sections (overtones) and a distinct sound sensation will be interpreted for each instrument

THE HUMAN EAR

The human ear, like that of other mammals, is made up of an external, a middle, and an inner ear

The External Ear

The external ear consists of (1) the *pinna* or *auricle*, the structure external to the skull and having little function in humans, and (2) the *external canal* or *external auditory meatus* which leads from the pinna to the *tympanic membrane* or eardrum (Figure 165)

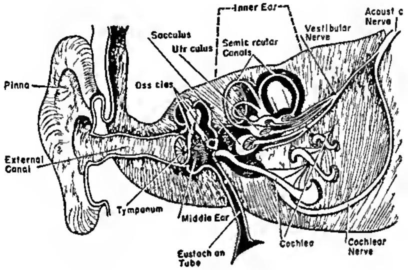


FIGURE 165

Diagram of external middle, and internal parts of the human ear

In most mammals the pinna is a horn shaped structure provided with muscles that enable the animal to move it in various directions as an aid in locating the source of a sound The pinna, therefore, has two chief functions to ascertain direction of sound, and to concentrate the sound waves into the external canal In humans, obviously, the loss of the pinna causes no great difficulty in locating the origin of a sound

The *external*, or *auditory*, *canal* is about 1 in long and is surrounded largely by cartilage For the most part, it is directed inward and very slightly upward toward the tympanum which closes its internal end Numerous glands are found on the surface of the skin lining the canal, these secrete a yellow waxy substance called *cerumen* which is lubricating and protective in its function Along with the hairs it prevents particles from getting too far into the ear Also, because of its odor, it acts as a repellent to insects so that they are less likely to enter into the auditory canal

The Middle Ear

The middle ear consists of a rather irregular chamber in the temporal bone (Figure 166), separated from the external canal by the tympanic membrane. The inner wall of the cavity has two perforations, the *round* and *oval windows* (*fenestra rotunda* and *fenestra ovalis*, so named because of their shape), which lead into the inner ear; these are covered by a delicate membrane. An opening, the *Eustachian tube*, leads from the middle ear to the pharynx. Within the middle ear are the three ear bones or ossicles: the *hammer* (malleus), the *anvil* (incus), and the *stirrup* (stapes). These linked to one another, in a chain, by very small ligaments form a connection between the tympanum and the membranous covering of the oval window. Their function is obviously to convert the sound vibrations into vibrations within the fluid of the inner ear.

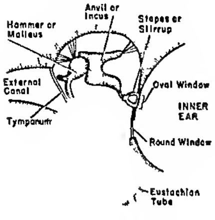


FIGURE 166

The middle ear and its ossicles

The malleus is connected at one end with the drum membrane and, at the other, articulates with the incus which in turn articulates with the stapes. They act together in the manner of levers, but in such a way that the amplitude of the movements of the stapes in and out of the oval window is much less than that of the drum itself; the force, however, is increased. The vibrations of the stapes cause vibrations in the perilymph of the inner ear and the shock is absorbed by the movements of the membrane covering the round window (Figure 165).

One type of middle ear deafness is produced by ossification at the articulations of the bones. The *eardrum* or *tympanic membrane* picks up all sorts of vibrations and transmits them by way of the ear bones to the inner ear. This membrane is stretched across a cartilaginous ring surrounding the inner end of the external canal and consists of three layers. The middle layer is composed of fibrous tissue, the fibers of which run chiefly in a radial direction, although some occur at various angles. This may account for the aperiodic response (vibrating unselectively to a wide range of frequencies) of the membrane to sounds. The other two layers are the mucous membrane, located internally, and the skin, externally. Altogether, these layers are about 0.1 mm thick.

The Eustachian Tube and Its Function. The Eustachian tube or canal

is about 35 mm long and connects the middle ear with the pharynx If the middle ear were entirely closed, movements of the stapes in and out of the oval window and the consequent movement of the membrane of the round window would be difficult The result of such a condition is often noticed by persons suffering from head colds when the Eustachian tube is also affected If the tissues of the latter become swollen the tube does not open to allow equilibrium between the air in the cavity and that external to it, temporary partial deafness may result

Normally, the tube is closed in order to prevent the usual respiratory movements from affecting the middle ear cavity These movements would be heard as loud noises if the tube were always open, it can be opened at any time, however, by the act of swallowing Thus when one enters a tunnel where the atmospheric pressure is greater than that outside, the tympanic membrane is forced inward (the pressure in the middle ear cavity is still equal to that outside the tunnel) and a sensation of fullness in the ears is experienced, by swallowing the air pressure within the cavity is brought to an equilibrium with that outside, causing the tympanum to take its normal position

The tube is lined by smooth muscles which keep it closed most of the time, their tension is released, however, by swallowing and thus the tube opens If the difference between the inside and outside pressure is very great, the tube wall collapses and there is danger of the drum rupturing This condition is liable to occur in a person failing to swallow often enough while descending in an airplane, the external pressure becomes so much greater than that in the middle ear, that the tube remains collapsed This is unusual in a conscious individual but it has happened in unconscious persons

The Eustachian tube is an essential structure for normal sound reception but it is also an opening by means of which infectious organisms can make their way to the middle ear and the mastoid process causing middle ear infection or mastoiditis

The Inner Ear or Labyrinth

The round and oval windows open into another cavity within the temporal bone the inner ear which has many extensions Because of its shape it is called also the *bony* or *osseous labyrinth* The three different portions of this cavity are referred to as the *vestibule*, the *cochlea* and the *semicircular canals* Within the cavity of the bony labyrinth is a fluid called the perilymph, and suspended in it by ligaments and fibers is the *membranous labyrinth* This membranous labyrinth extends through the several parts

of the bony labyrinth and is filled with endolymph. Within the vestibule are two saclike, connected enlargements, the *sacculus* and *utriculus*. An extension of their connection forms the *endolymphatic duct*. From the utriculus the three *semicircular canals* extend through the cavities of the bony labyrinth which bear the same name. The *cochlear canal* extends from the sacculus up through the cochlea (see Figure 167).

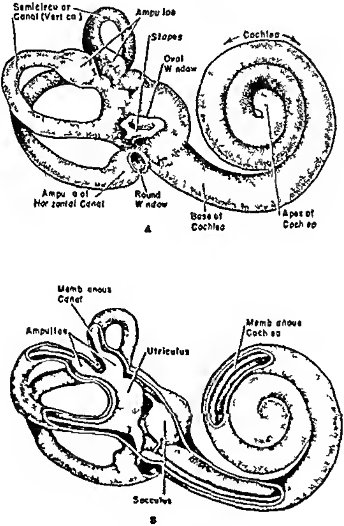


FIGURE 167

The labyrinth or inner ear. A, cast of bony labyrinth. B, same with parts cut away to show membranous labyrinth within.

The diagram presented in Figure 168 indicates the direction of the movements of waves produced by vibrations of the stapes. They travel through

out the perilymph which completely surrounds the membranous cochlea In this figure the cochlea is shown as though it were uncurled and stretched out By this means one can understand how the movements of the peri lymph travel up the *vestibular canal* (*scala vestibuli*) which leads directly from the vestibula to the apex of cochlea and back down the *tympanic canal* (*scala tympani*) to the round window whose membranous covering reacts to

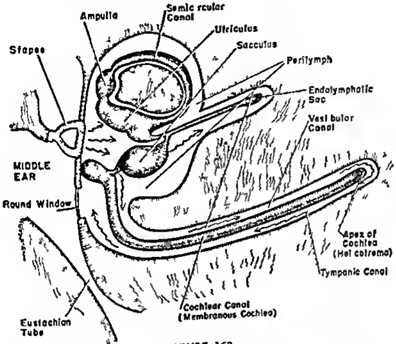


FIGURE 168

Diagram of the inner ear illustrating the manner in which the sound waves travel in all directions through the perilymph The cochlea is shown as it would appear if stretched out

the lymph movements by bulging outward or inward whichever is necessary to equalize the pressure

The tympanic canal has no connection with the tympanum or eardrum as the name might imply but is simply a continuation of the vestibular canal by means of which sound waves are transmitted through the cochlea

Sometimes overstimulation of the ear structures by sound will affect the organs of equilibrium (sacculus utriculus and semicircular canals) so that one may become dizzy

The Membranous Cochlea The membranous cochlea (*scala media* or cochlear canal) is a tube about 30–32 mm long and it is wound around a bony central core called the *modiolus* (Figure 169) The cross section shows that the cochlear canal is partly bounded by the bony side wall Its

other boundaries are *Reissner's membrane* and the *basilar membrane*. The basilar membrane is attached to the bony shelf (*spiral lamina*) on one side and the bony side wall on the other. This also applies to Reissner's membrane. The two are arranged so that a triangle is formed when viewed in cross section. That portion of the cochlea above the cochlear canal is

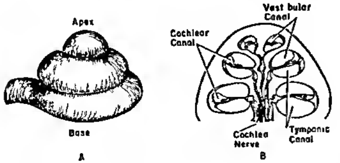


FIGURE 169

A plaster mold of cochlea. B section through the center of the cochlea with various structures designated.

called the *vestibular canal* whereas, beneath the cochlear canal is found the *tympanic canal*. These two are continuous at the apex of the cochlea as is shown in Figure 168.

If the cochlear canal is magnified in cross section, several very interesting structures are visible (Figure 170). The basilar membrane is found to be made up of many fibers running radially to the modiolar axis of the cochlea

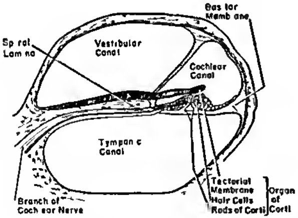


FIGURE 170

Enlarged diagram of cochlear canal in cross section.

when viewed from the apex. Their number has been estimated at 24,000. They are arranged in parallel formation, and from the base of the cochlea to its apex these strings or fibers become progressively longer (Figure 171), the shorter fibers at the base are about 40 microns long, those at the apex about 500 microns. It is of interest to note that the basilar membrane is in direct contact with the perilymph of the tympanic canal and, therefore, is exposed to the effects of the vibrations produced in the fluid of the canal.

The Organ of Corti The *organ of Corti* is found on the basilar membrane and runs the whole length of the cochlear canal Suspended above it is the *tectorial membrane*, which is attached at one end but free at the other, and is probably in contact with the hair cells

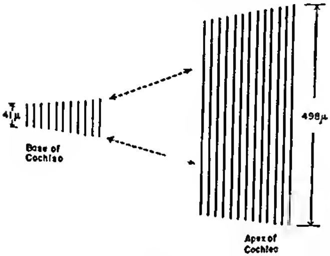


FIGURE 171

Diagram to show the comparative lengths of the fibers of the basilar membrane at the base and at the apex of the cochlea

The cells of the organ of Corti in direct contact with the basilar membrane are very peculiar, they are rod shaped (*rods of Corti*) and are joined at one end but separated at the other forming a tunnel (*tunnel of Corti*) The rods separate the *hair cells* into a single row of *inner hair cells* and three

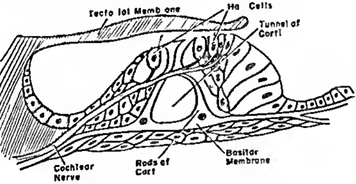


FIGURE 172

The Organ of Corti of the human cochlea

or more rows of *outer hair cells* There are about 2500 inner and about 13 000 outer hair cells which are evidently stimulated by their contacts with the tectorial membrane Upon stimulation of these by vibrations impulses are sent from them over nerve fibers of the auditory branch of the acoustic nerve to centers in the temporal lobe

The Resonance Theory of Hearing

Helmholtz, long ago, proposed the so called "resonance theory" of hearing He judged that the basilar membrane consisting of numerous fibers of different lengths (the longest at the apex, the shortest at the basilar turn of the cochlea) acted as a resonator when played upon by vibrations in the perilymph The "strings" of the basilar membrane vibrate, according to Helmholtz, like the strings of a piano The strings or fibers which are set into vibration depend upon the pitch of the sounds picked up If the sound is of low pitch, resulting in a few vibrations per unit time, the basilar fibers at the apex of the cochlea are set into vibration in the same manner that a vibrating tuning fork of low pitch will set one of the bass strings of a piano into vibration A sound of high pitch will accordingly affect the shorter fibers at the base of the cochlea There is considerable difference, however, between the strings of a piano and those of the basilar membrane In the latter they are held together by connective tissue and hence tend to "dampen" one another, that is, the fibers of the basilar membrane do not continue to vibrate after the sound waves have ceased, whereas the strings of a piano will continue to vibrate In spite of this, evidence is strongly in favor of some sort of resonance theory Upon clinical examination of the cochlea of the ears of persons who have suffered from partial deafness during life, it was found that those who were deaf to sounds of low pitch showed lesions in the "organ of Corti" at or near the apex On the other hand, in the cochlea of those who have suffered from high pitch deafness, lesions were found at the base The same type of results were obtained in animals in which parts of the cochlea had been experimentally destroyed

Vibrations are set up in the perilymph of the inner ear and proceed up the vestibular canal It is doubtful that normally they have any effect on the true end organs from this direction Reissner's membrane is not specialized in any way that might suggest its function as a vibrating organ—it probably functions as a protective structure At the apex of the cochlea, however, the vestibular canal joins with the tympanic canal (the point of union is known as the *helicotrema*) The vibrations are, therefore, continued through the tympanic canal and may have a direct effect on the basilar membrane of the cochlear canal, that is, the basilar fibers which are affected by the particular pitch will vibrate The hair cells on the organ of Corti at that point are stimulated by their movement against the tectorial membrane and impulses pass over the nerve fibers to the association areas of the brain

Deafness

Any part of the hearing mechanism may be affected by disease or injury that may lead to partial or total deafness. There are several types of deafness. (1) *Transmission or conductive deafness* is caused by interference in the passage of sound vibrations in the external or middle ear. Ear wax, or other foreign bodies in the external canal, *ankylosis* (adhesions) of the middle ear bones, or pressure differences may be the direct cause of transmission deafness. Since the end organs and nerves are still intact in this type of deafness, a person is capable of hearing by means of bone conduction or hearing aids. (2) *Perceptive deafness* may result from injury to the "organ of Corti," or from injury or disease of the auditory nerve. In this case, hearing aids are not very useful. (3) *Central deafness* is caused by lesions in the auditory pathways in the brain or the auditory center of the cortex proper. This type of deafness also is not responsive to hearing aids.

Equilibrium. Static Organs of Invertebrates

Organs of equilibrium, or static organs as they are sometimes called, are tissues that function in the equilibrium or position of a body of an organism with regard to gravity or position in space. They function in the same manner as tactile structures but are much more delicate. As specialized organs they are usually supplied with sensitive "hair cells" which are acted upon by the pressure of small calcareous or siliceous bodies called *otoliths* or *statoliths*. These sensitive cells may also be acted upon by the pressure produced by movement of the endolymph.

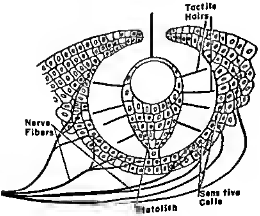


FIGURE 173

The static organ of a coelenterate medusa. The statolith sways with movement and the tactile hairs stimulate the sensitive cells by pressure against them.

From an evolutionary viewpoint, one of the earliest types of structures concerned with equilibrium is found in the medusae of some coelenterates

Specialized organs (*statocysts*) are found along the rim of the umbrella (Figure 173) They are supported by narrow stalks which allow the structures within the cavity to sway, and the hairs protruding from the cells are forced against the side walls This is the principle involved in all specialized static organs

Most invertebrates do not have such specialized static organs In many cases animals depend upon touch sensation for ascertaining position in space

The arthropods have well developed organs of equilibrium and some interesting experiments have been carried out with certain species of crustaceans The crayfish for example has saclike organs at the base of each of its antennules The cavities of these structures are lined with hair (ciliated)

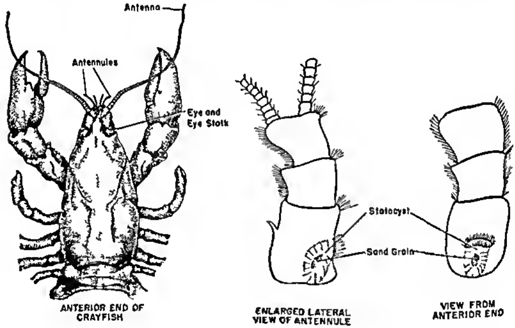


FIGURE 174

Illustrating the positions of antennules and the organ of equilibrium (*statocyst*) of the crayfish

cells and contain grains of sand which, moved by force of gravity, stimulate the hair cells, each of which is supplied with a neuron When the crayfish molts and throws off its chitinous exoskeleton so that it can grow, these sand grains are lost and the animal must pick up others and place them in the sac If iron powder is placed in the statocyst instead of the sand grains immediately after the exoskeleton is discarded, the crayfish has no great difficulty in maintaining its equilibrium or in moving about from place to place

The iron, however, can be made to take almost any position in the statocyst by means of a magnet. If the magnet is applied to the right side of the statocyst, the iron filings contact the hairs on the right side, which produces the same effect as when turning or falling on the right side The crayfish, reflexly, turns on to its left side in an attempt to "right" itself If the magnet is held above the crayfish, it is forced to swim on its back

Insects have the power to maintain equilibrium very well and certain specialized structures have been found which have this function However,

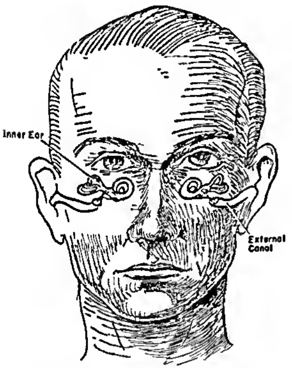


FIGURE 175

Showing the relative positions of the cochlea and semicircular canals in the human

the majority of studies, up to the present time, have been concerned with equilibrium of flies in flight The rudimentary wings (behind the true wings) are called *halteres* or balancers and are thought to function as organs of equilibrium Some flies can get along just as well without the balancers, whereas others lose their equilibrium in flight if the halteres are removed

Organs of Equilibrium in Vertebrates

Specialized organs of equilibrium are found in all vertebrates Those of mammals have been investigated more thoroughly than those of any others The structures involved in equilibrium and posture are the *semicircular canals* and the *utriculus* and *sacculus* of the inner ear (Figure 175, also Figures 167 and 168) Two of the semicircular canals are vertical

(anterior and posterior), standing at right angles to each other, the third is horizontal At one end of each, just before it enters the utricle, is an enlarged sac or chamber, the *ampulla* (see membranous semicircular canals) The special receptors are found in the ampullae and consists of a group of

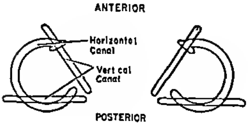


FIGURE 176

Normal position of semicircular canals in the head as viewed from above

hair cells which connect with neurons from the vestibular branch of the eighth cranial nerve These end organs are called *cristae*, and are acted upon by the change in force of the endolymph in the semicircular canal, when the head is moved with an increased or decreased velocity, or suddenly in a new direction

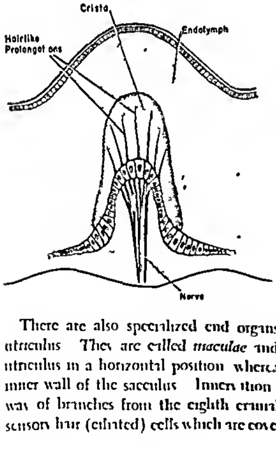


FIGURE 177

Enlarged view of the ampulla of a semicircular canal showing the functional end organ the crista

There are also specialized end organs found within the sacculus and utriculus They are called *maculae* and are located on the floor of the utriculus in a horizontal position whereas they are almost vertical on the inner wall of the sacculus Innervation of these structures occurs also by way of branches from the eighth cranial nerve The maculae consist of sensory hair (ciliated) cells which are covered with a gelatinous material con

taining many calcareous crystals These crystals (otoliths or statoliths) are moved by force of gravity as the head changes its position and in this manner may "pull" on or "press" against the hairs or cilia

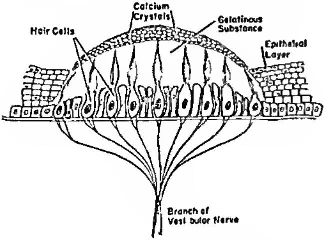


FIGURE 178

A macula the equilibrium organ of the human utriculus

In other words, there are evidently two processes involved (1) that concerned with *dynamic equilibrium*, or the movement of the head (and body) through space, and (2) that concerned with *static equilibrium*, or the position of the head (and body) in space

The semicircular canals function in dynamic equilibrium As the head moves, the canals move in the same direction, but the endolymph, because of its inertia, is displaced slightly in the opposite direction, and the hairs (cilia) of the end organs are thus bent to produce a sensation In this manner, information is gained as to the direction of movement, usually, the eyes, muscles and tendons also contribute to the sensation of movement

The maculae of the utriculus and sacculus are in a normal position when the head is erect Only when the position of the head is changed, do they send impulses to the brain For example, if a person should stand on his head, the calcareous granules would then be pressing against hairs that they previously had been pulling and vice versa Such stimulation serves to inform one that he is "upside down" in comparison to his normal position These organs are similar in their action to the static organs of the

Part Five

The TRANSPORT SYSTEM

20

The Fluid Media of Animals

TRANSPORTATION OF SUBSTANCES WITHIN ANIMALS

THE TRANSPORT SYSTEM in animals is dependent upon the fluid media The only way in which food oxygen and other materials can get into and waste products can get out of cells is by diffusion through cell membranes In the most primitive of animals the *Protozoa* no special system for transportation of these substances is needed unless streaming movement of the protoplasm which aids in circulation within the cell might be considered as a primitive transport system These single celled organisms come in direct contact with their environment thus obtaining food and oxygen directly from it In the *Porifera* (sponges) and *Coelenterata* (hydra jellyfish and similar invertebrates) approximately the same condition exists since the cells of these forms also come in direct contact with their environment

In large animals with tissues consisting of many layers of cells those cells lying deep within the body would soon die of suffocation and starvation unless a special means of transportation were available diffusion could not otherwise extend into these layers The fluid media of animals therefore show a gradual development from the primitive situation of those organisms requiring no special medium at all to the advanced situation of those requiring highly complex circulating media as well as circulatory organs for carrying the fluids to and from various tissues and organs

CLASSIFICATION OF FLUID MEDIA OF ANIMALS

Most of the circulating or fluid media of organisms belong to one of the following types

1 *Water* is the only medium that surrounds the cells of such forms as *Protozoa Porifera* and *Coelenterata* their natural environment covering a rather large area such as the sea lakes or ponds Water carries oxygen and food substances necessary for the life of these forms and the waste products need merely pass through the cell membranes into the water

2 *Hydrolymph* as the term suggests is a watery fluid carrying nutriment to and removing wastes from organs and tissues of lower animals This type of medium contains no *respiratory pigments* (hemoglobin or hemoglobin like compounds) and therefore has no respiratory function except for the

oxygen carried by the medium itself However the hydrolymph in the water vascular system of *Echinodermata* (starfish) carries oxygen in sufficient quantity to supply the tissues of these organisms In addition to being present in the echinoderms hydrolymph is found also in flatworms

The transport medium of some echinoderms (sea cucumbers) however contains hemoglobin like pigments within cells or corpuscles and therefore possesses a specialized respiratory function These are the lowest forms of animal life in which a respiratory pigment is carried within cells Aside from these few exceptions the presence of red blood corpuscles seems to be confined to the vertebrates

3 *Hemolymph* is a circulating fluid that has a greater protein content than hydrolymph and is less watery The media falling into this group contain hemoglobin like substances that are dissolved in the plasma and sometimes correspond closely to hemoglobin of higher organisms these substances or pigments are very seldom present in corpuscles This type of fluid occurs in *Annelida* (earthworms) and *Mollusca* (oysters)

4 *Tissue fluid* is usually derived from the blood by means of filtration or dialysis through the blood capillaries It is the fluid in direct contact with the cells of the bodies of organisms and conveys foods oxygen and other materials from the blood to the cell It is therefore a fluid that is found in the intercellular spaces of all animals (except protozoan forms)

5 *Lymph* is usually described as a liquid derived from vertebrate tissue fluid and is similar to it except that it is contained in vessels (lymphatic vessels) The circulating media of some species of animals containing no respiratory pigments in their body fluids have lymphlike characteristics

Insect lymph is often referred to as blood since it is actually lymphlike in its structure In insects the general body cavity is a lymph sinus called a hemocoele Most of the respiration is carried on through tracheal tubes which leading directly to the tissue cells take oxygen to and remove carbon dioxide from the tissues Except for a few larval forms (for example *Chironomus* a midge larva) insect blood contains no respiratory pigment Colorless cells called *hemocytes* are present and move about from place to place These cells are phagocytic (they attack bacteria and other parasites in the lymph or blood) and function chiefly in (1) breaking down old and building up new tissue and (2) protecting insects against bacterial invasion

Unlike the blood of vertebrates the lymph of insects is not under very great pressure actually showing in some cases a negative pressure Thus loss of fluid as a result of injury is not a serious problem to these animals and therefore clotting of the blood is not nearly so important as in those with

great blood pressures If some of the body fluid of insects tends to escape from a small injury, it may dry rapidly and form a protective film over the opening or, in some cases, the colorless cells may collect at the opening to prevent further outflow

6 *Blood* is the chief circulating fluid of all vertebrates In these forms the fluid has taken on the characteristics of a tissue and is treated as such It is a very complex fluid, more so than any of the other types found in animals

FUNCTIONS OF VERTEBRATE BLOOD

For the present, most of our discussion will be reserved for the blood of vertebrates As a transportation medium it has a variety of functions (1) It has a *respiratory function* in that it carries oxygen to the tissues (2) It has an *excretory function* in carrying *carbon dioxide* to the alveoli of the lungs and *other waste products* to the kidneys skin, and intestines for disposal (3) It *distributes heat* uniformly over the body and thus aids in equalizing and controlling temperature (4) Its *nutritive function* is also a highly important one, the body cells cannot live very long without proper food material The blood can pick up materials absorbed through the intestinal wall and distribute these to the points where they are needed (5) It *carries hormones*, or internal secretions, which regulate and coordinate many bodily processes (6) It provides for proper *water distribution* throughout the body (7) It *defends the body* against the inroads of disease producing microorganisms This is accomplished in one or both of two ways (a) phagocytosis, and (b) formation of immune bodies (8) By its *ability to clot*, the blood is protected from too great a loss in volume when the vessels which carry it through the body are injured (9) It furnishes a *physiologically balanced medium* for the tissues of the body (10) It contains materials rendering it an excellent *buffer medium* so that the reaction of the blood and tissue fluids may be maintained at their normal level, that is, near neutrality

THE COMPOSITION OF THE BLOOD

The average specific gravity of human blood is about 1 055, and its *p*H is between 7 4 and 7 43 for arterial, and 7 35 and 7.4 for venous blood Its viscosity is two to five times that of water The volume of the blood normally occupied by the red blood corpuscles may vary considerably—between 40 and 50 per cent The volume of the liquid part, or plasma, varies inversely with the corpuscle volume

If a drop of blood is examined under the microscope it is found to consist of innumerable minute cells (**corpuscles**) suspended in a liquid (*plasma*)

Two kinds of blood cells can be distinguished the vast majority are disc shaped red corpuscles, or *erythrocytes*, scattered among these are the white or colorless corpuscles, *leucocytes*, which unlike the red cells, have retained their nuclei If proper precautions are taken, a third type of corpuscle may be seen, the *blood platelets*

The Blood Plasma

The plasma is a very complex fluid consisting of many substances associated with proper functioning of the blood Plasma is composed of approximately 90 per cent water and 10 per cent solids The solids are chiefly organic compounds although about 1 per cent of the plasma consists of inorganic salts especially the chlorides, sulfates, carbonates and phosphates of sodium, potassium, calcium, and magnesium

The Blood Proteins

The blood proteins *serum albumin serum globulins*, and *fibrinogen*, make up about 7 per cent of the plasma These proteins have several functions as follows (1) *Maintenance of proper water balance* between the blood stream and the tissue fluid This is accomplished by proper osmotic relationship on either side of the smallest blood vessels (the capillary membrane) In other words, if the protein content of the plasma is too great compared with that of the tissue fluid, too much water may be drawn from the tissues, or if the osmotic pressure is greater in the opposite direction, too much water may enter the tissues, a condition known as edema or *dropsy* (2) *Fibrinogen* plays a part in the process of *blood coagulation* It is soluble in the plasma but, during the processes concerned with blood clotting, it is changed to the insoluble fibrin (3) All the proteins aid in producing a *viscosity* in the blood most favorable for the maintenance of blood pressure at a normal level (4) Of the serum globulins, the *gamma globulins* appear as normal constituents and also in a form wherein they act as antibodies—immune bodies produced in special tissues in response to the presence of foreign substances, such as bacterial toxins, and released into the blood stream

Many nonprotein substances, also containing nitrogen in their molecule, occur in the plasma Such substances as urea creatine creatinine, uric acid ammonium salts, and amino acids are of this type, they vary considerably in concentration

There are present several *nonnitrogenous compounds* such as glucose (0 09 to 0 1 per cent normally), fats and lipoids

In smaller quantities we find the hormones (chemical coordinators),

enzymes, prothrombin which is also concerned with coagulation, and various gases These gases (oxygen carbon dioxide, and nitrogen) are dissolved only to the extent that they would be dissolved in water under the same conditions Most of the oxygen in the blood exists in combination with hemoglobin and most of the carbon dioxide, as bicarbonate of sodium or potassium When the blood reaches the tissues carbon dioxide is taken on as a waste product and is eliminated in the lungs Extreme changes in the acidity of the blood would take place, if it were not for the presence of proteins, and phosphate and carbonate salts, in the plasma As buffer substances, they have the capacity of neutralizing the effects of hydrogen ions and hydroxyl ions by combining with them temporarily These ions are then eliminated by way of the excretory organs

THE VOLUME OF THE PLASMA AND WHOLE BLOOD

Whole blood is about 9 per cent of the total body weight, and plasma, about 5 per cent The average man (70 kg or 155 lbs) has, then, approximately 6 liters of blood Infants have a greater blood volume in proportion to body weight than adults, although the proportion of blood volume to body surface is lower in the infant than in the adult

Actually, the volume of all body fluids including blood are dependent upon one another Therefore, the blood volume and its changes cannot be understood without considering at the same time, the total fluid content of the body

a rather stationary mass in comparison with blood and lymph, nevertheless there are very few parts of the body into which the blood is not carried and therefore, since distances are not very great, diffusion of substances from the blood into the tissue cells is almost direct Very important structures, such as voluntary muscles and the walls of the intestinal tract, have a rich supply of blood capillaries in order to ensure rapid diffusion of food materials and oxygen into the muscles, as well as food materials from the intestines into the blood The brain lungs, and heart muscles are also well supplied with blood

Some regions of the body have no direct blood supply For example cells on the inner area of the epidermis (the outer layer of the skin) (Figure 115, page 193) must depend upon materials from the tissue fluid bathing the dermal cells However, as is generally known, the epidermal cells do not show very great metabolic activity and therefore, are not in need of very large supplies of oxygen and food

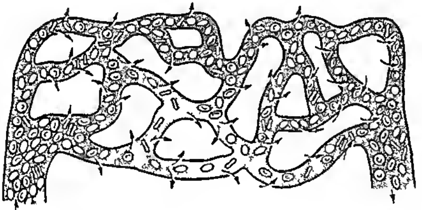
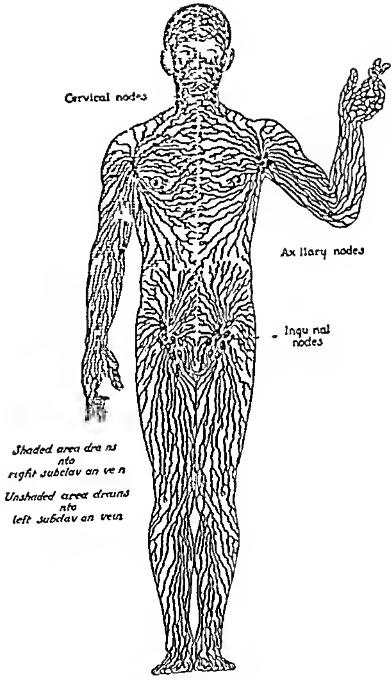


FIGURE 179

Diagram illustrating the diffusion of plasma materials into tissues on arteriole side of capillaries Because of a lowered osmotic pressure in the blood capillaries some of this fluid passes back into the capillaries on the venous side Arrows indicate direction of diffusion

The tissue fluid is constantly changed although, normally, very slowly As pointed out above it is formed by the continuous flow of water and other substances from the plasma through the capillary membranes into the tissue spaces This flow takes place on the arteriole side of the blood capillaries This tissue fluid for the most part is returned to the blood stream by way of the lymphatic system It first passes through the walls of the lymph capillaries and joins the lymph stream which flows into successively larger lymph vessels which empty into the large veins near the neck region



Cervical nodes
Ax llary nodes
Ingu nal nodes
Shaded area dra ns nto right subclav an ve n
Unshaded area drains nto left subclav an vein

FIGURE 180

It is evident that diffusion, osmotic, and filtration phenomena play an important part in nutritive and respiratory processes of the body. By these various means the blood gains dissolved food materials while passing through the capillaries of the digestive tract and loses them to the tissue fluid in other parts of the body where they are needed. At the same time that digested foods (and oxygen which was taken on in the lungs) are passing from the blood capillaries to the tissue fluid waste products are passing from the tissue fluid into the blood. Thus what the blood loses in one region it gains in another, and vice versa.

Structure of the Lymph System

The lymph system has its origin in a meshwork of closed lymph capillaries which begin blindly in the tissue spaces and in the *villi* or finger-like projections that give greater surface to the intestines. This network of lymph vessels is about as extensive as the capillaries of the blood system. Excess

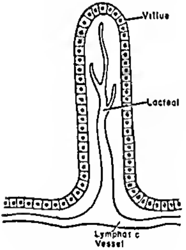


FIGURE 181

Lymph capillary and lacteal leading into intestinal villus. Arteriole, capillaries, and venule not shown.

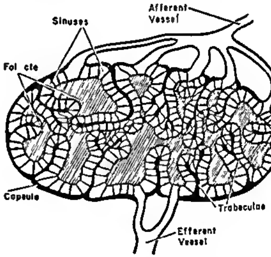


FIGURE 182

Structure of lymph gland or node

tissue fluid collects in these lymph capillaries where it is known as *lymph* and from where it is carried back by larger lymph vessels to the blood stream as mentioned above. The lymph capillaries of the intestinal villi are called *lacteals* because the fatty materials that are absorbed into them give a milky appearance to the fluid.

The lacteals unite with others to form larger lymph vessels which unite

successively to form still larger ones The course of the larger vessels being interrupted occasionally by *lymph nodes* or *lymph glands* generally follows that of the veins These glands have sinuses into which the smaller vessels empty The contents are again collected into afferent vessels leading away from the nodes All of the lymph from the arms and legs must pass through at least one of these nodes on its route to the blood vessels Each lymph node or gland functions as a filter for foreign organisms and particles Finally, all of the vessels unite to form two main branches the *right lymphatic* and the *thoracic ducts* The right lymphatic duct is formed by lymph vessels from the right side of the head neck and thorax the right arm, right lung and right side of the heart and the convex surface of the liver All other lymph vessels eventually empty into the larger vessels leading to the *thoracic duct* These branches connect with the blood stream in the neck region via the right and left subclavian veins, respectively, and the lymph is mixed with the blood at these points

Lymph vessels are lacking in some structures in the body including the central nervous system, the alveoli of the lungs the bone marrow, and the pulp of the spleen

The volume taken up by the lymph is not known but is thought to be less than that of the blood Lymph clots slowly, since it contains rather small quantities of those substances needed for clotting that is, prothrombin and fibrinogen

OTHER BODY FLUIDS

The *peritoneal fluid* is found in the cavity formed by the walls of the peritoneum in the abdomen

The *pleural fluid* occurs in the pleural cavity of the thorax, in which the lungs are situated

The *pericardial fluid* is present in the pericardial cavity, in which the heart is located

All of these fluids present only as films are probably derived from tissue fluid and function in the lubrication of the walls of the body cavities The organs surrounded by these fluids can therefore move much more freely since no great friction is produced by their movement

The fluids of the eye, the ***aqueous humor*** and the fluid of the *vitreous body* function in the retention of the shape of the eye at the same time allowing light to pass to the end organs at the back of the eye, they are called *intraocular* fluids

The *perilymph* and *endolymph* of the inner ear function in the protection of the membranous cochlea and in the transmission of sound waves

The *cerebrospinal fluid* is found in the subarachnoid space of the brain and spinal cord and also in the ventricles of the brain and the central canal of the cord.

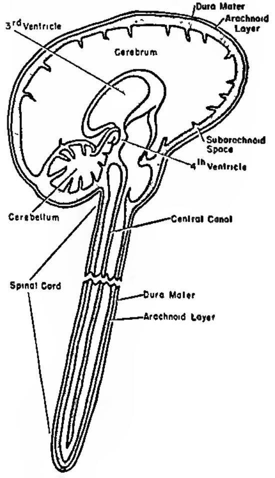


FIGURE 183

Diagram of central nervous system indicating spaces in which cerebrospinal fluid is found

The pia mater, a membranous coat in direct contact with and completely surrounding the brain and cord, ends with the cord at about the level of the first lumbar vertebra. (See also discussion on page 141.) The dura mater and the arachnoid layers extend to about the second sacral vertebra, the subarachnoid space being very large in this region. For that reason, if a hollow needle is carefully inserted into this space, cerebrospinal fluid can be drawn off readily. This procedure is known as *lumbar puncture.*

If the outflow of cerebrospinal fluid, formed in the ventricles of the brain, is blocked, the result is *hydrocephalus,* an enlargement of the brain and skull in very young children. Cerebrospinal fluid is very similar in composition to tissue fluid and lymph; its total volume is 120 to 130 cc. and it forms at the rate of about 0.5 cc. per minute. It probably acts as a mechanical

buffer or cushion to prevent injury to the brain or cord. It also has a nutritive function, being kept in motion by means of cilia in the ventricles.

FLUID EXCHANGE IN THE BODY

A constant interchange of fluid takes place between the tissues and the blood. Whenever conditions arise that tend to increase or decrease the water content of the blood and therefore to raise or lower the volume some mechanism functions in counteracting these changes. Fluid lost from blood vessels is restored by the passage of water from the tissue spaces into the blood stream. Also, if conditions are such that blood volume rises the excess fluid is poured into the tissues or is excreted. In this manner, a balance between the blood volume and the tissue fluid volume in the healthy individual is maintained at a rather constant level.

The fact that the circulation draws upon extravascular spaces when in need, may be demonstrated on an animal that is bleeding to death because of a severed artery. Samples of blood obtained at different times during the bleeding, are analyzed. The samples secured after a few minutes of bleeding contain fewer corpuscles per unit volume than those taken when the artery was first opened. Chemical analyses of the later samples show also a great decrease in concentration of plasma proteins and other substances. This is clear evidence that the blood is diluted by fluids diffusing into the blood stream from the tissues. This diffusion occurring almost simultaneously with the decrease in blood volume is a natural attempt to overcome that decrease.

REPLENISHMENT OF WATER IN BODY FLUIDS

Normally, water in the body fluids may be replenished in two ways (1) by the drinking of liquids or by ingestion of foods that contain water, and (2) by *metabolic water* formed during oxidation of foodstuffs. In the following table are presented the quantities of metabolic water formed by the oxidation of the three main classes of foods and of alcohol.

TABLE 5

Amount of Metabolic Water Produced by Designated Compounds

Compound Oxidized	*Grams of Water Produced Per 100 Grams of Substance Oxidized*
Alcohol	117.4
Fat	107.1
Starch	55.1
Protein	41.3

In the average man, from 300 to 350 g. of water are produced daily in this manner.

Foods stored in the bodies of animals or in the body tissues themselves can furnish water by this method when none is taken directly or contained in the food ingested. Glycogen, protein, and fat stored in the body can, upon oxidation, produce fairly large quantities of water. The camel's hump, actually a reservoir, contains much fat. The fat is held in reserve until such time when the camel will be unable to find pure water in its environment. The fat is then oxidized and the water thus formed is available for the camel's needs.

Very interesting experiments have been made upon clothes moths with respect to the production of metabolic water. The material they normally use as food contains very little water, and moths have never been known to drink water. If they are placed in desiccators and fed perfectly dry food, they lay eggs which are 80 per cent water. This water could be obtained only by oxidation of food materials.

The cases just cited are extreme, to be sure, but we know now that the very same kinds of oxidative processes will also furnish man and other mammals with much needed water. The amount that can be furnished and utilized, however, is limited.

LOSS OF WATER FROM THE BODY

Water may be excreted from the body in several ways: via the urine of the kidney, the feces of the alimentary tract, the sweat of the skin glands, and the expired air of the lungs. Sometimes there is considerable loss by way of saliva, especially from the body of one who chews tobacco habitually. Usually, however, the water in the saliva passes on through the alimentary tract and appears along with that of the feces, or, if reabsorbed, it may appear in the urine or sweat—there would be no method of detecting it except by means of "tagged" molecules (molecules that have radioactive elements attached to them).

Table 6 presents the daily loss of water and the channels through which it is lost by the average man performing light work in a temperate climate.

These figures vary considerably from person to person and in any particular locality depend upon food and liquid intake, temperature, humidity, and muscular exercise. Much more water is lost as sweat at high than at low temperatures. When humidity is high, more is lost via the urine than when the humidity is low. Although one appears to sweat more in high humidity, it is merely due to the fact that the sweat does not evaporate very rapidly. In hot climates the daily sweat secretion may amount

TABLE 6

Loss of Water from Body of an Average Man
(average temperature and humidity in temperate climate)

Water Lost by Way of	*Average Daily Loss (in cc)*
Skin	500
Expired Air	350
Urine	1500
Feces	150
Total	2500

to 2500 cc or more and in very torrid regions to 10 liters or more. This loss requires ingestion of an equal quantity of water if the intake and output are to balance. The ratio is held at a constant level except during growth (or during convalescence from disease) when more water is taken into the body than is eliminated. This can be explained by the utilization of water during the process of protein formation from amino acids—a process necessary to rebuild weakened or worn tissues.

During muscular exercise there may be large quantities of water lost by way of the sweat glands and lungs. Since, ordinarily, the air entering the lungs contains only small quantities of water, the expired air is saturated at lung temperatures. Thus, any increase in respiratory activity will also increase water loss.

The human body contains about 70 per cent water. If this water were extracted it would fill a 10- to 12-gallon container. The blood contains only a small part of the total body water—approximately one fourteenth of the total. Most of it is found in other tissues, such as muscle and epithelium, that make up a greater part of the bulk of the body. Almost all of the water is in the "free" state in which soluble substances can dissolve and it can be removed by *ultra filtration*.

If more than 25 or 30 per cent of the total body water is lost, the result may prove fatal unless immediate remedies, such as transfusions, are employed.

Many factors may be connected with water loss or dehydration: failure to obtain fluids, persistent vomiting, prolonged diarrhea, or an increase in osmotic pressure between the tissue fluid and the blood stream. This increase occurs when for some reason or other, the protein content of the blood is increased and therefore water is drawn from the tissue.

The effects of water loss are many. Perhaps the first to appear is thirst, and, if the factors causing the condition are not removed, a disturbance in

the acid base equilibrium appears, with a tendency especially toward a greater acidity Later, a definite loss in weight is noted along with a dryness and wrinkling of the skin These conditions result in the pinched expression so noticeable in persons convalescing from a long illness during which much of the body water has been lost

WATER INTOXICATION

Water intoxication, the opposite condition to water loss, can and does exist in animals When an animal is made to imbibe large quantities of water after the urinary output has been reduced by the action of pituitrin (see endocrines, Chapter 38), its tissues become clogged with water, and it is said to be *waterlogged* In man this is sometimes experienced when a person with *nephritic edema* is given large quantities of water Animals and man, if given large amounts of water, when suffering from cerebral edema may go into convulsions

EDEMA

Edema commonly called dropsy, is the term applied to excessive accumulation of fluids in the tissue spaces The condition is caused by a defect somewhere in the mechanism or mechanisms concerned with water balance in the body with the result that the tissues of the subcutaneous regions become swollen

Edema is known to develop as the result of abnormal activity of several processes (1) Reduction of osmotic pressure of the plasma by a decrease in protein content will cause water to flow from the plasma into the tissue spaces (2) An increase in the permeability of the capillary membrane will have the same effect (3) An increase in the pressure of the blood in the capillaries will tend to force more fluid into the tissue areas (4) Obstruction in the lymph channels is a factor, the effects being evident in elephantiasis, a disease caused by a species of small worm clogging the lymph vessels (5) Obstruction in the veins hindering proper flow of blood will cause a back pressure which will prevent any tissue fluid from passing back into the blood stream on the venous side of the capillaries

ADDITIONAL READING

Best C H, and N B Taylor *Physiological Basis of Medical Practice*, 5th ed (Baltimore Williams and Wilkins 1950) chs 1 3 4 Properties of blood and lymph water balance

21

The Red Blood Corpuscles

THE STRUCTURE OF THE RED BLOOD CORPUSCLES

THE RED CORPUSCLES, or erythrocytes, when examined under the microscope appear to vary in shape as they are carried along in the plasma, this variation being a result of the different angles at which they are viewed. Those that are seen as they lie flat on the slide appear to be circular, biconcave discs, hollowed out in the center. Often they pile up in the same manner as a stack of poker chips—a phenomenon known as *rouleaux* formation. The average transverse diameter of the wet erythrocyte is about 8 to 8.5 microns (or .008–.0085 mm.). Microscopic examination of blood cells is most conveniently carried out on dried and stained smears. On drying, a loss of 8 to 16 per cent in diameter takes place as the result of shrinkage. The average diameter of the blood cells, therefore, in dried smears is only approximately 7.5 microns. However, since comparisons are made for blood cells under the same circumstances, the shrinkage is of no great consequence in clinical practice. For example, the examination of a wet smear of blood obtained from a patient with pernicious anemia, shows that the red cells vary in shape and are much larger than the red cells of a normal individual. A dried smear of anemic blood when compared with a similar specimen of normal blood also shows proportionally larger red cells. The greatest thickness of the red cell is 2.4 microns and its least (measured at the centers of the concavities) is 1 micron. The total volume of the human erythrocyte is about 90 cubic microns—just small enough to pass through most capillaries in single file. At times, however, these cells appear to be squeezed through by contraction of the capillary wall. The red cells of most mammals are smaller than those of humans. The mature mammalian red cell contains no nucleus; the red cells of other

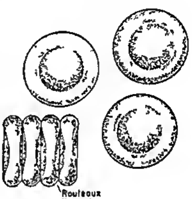


FIGURE 184

The human red blood cell

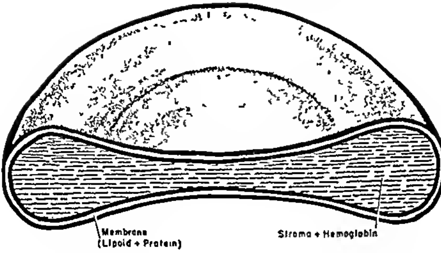


FIGURE 185

Cross section of red blood cell

mammals are circular also with the exception of those of the camel group, which are oval

The shape of the erythrocyte is most favorable for its chief function as an oxygen carrier It is a compromise between a sphere and a thin disc, the former shape is conducive to the greatest carrying capacity and the latter is most favorable for diffusion, since a greater surface is furnished

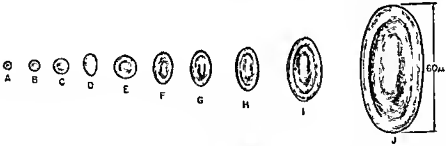


FIGURE 186

The red cells of various vertebrates illustrating their comparative sizes A, deer, B, goat, C marmot, D, camel, E, man, F, bird, G, fish, H lizard I frog J Amphiuma A–E, non nucleated (mammals), F–J, nucleated

Structurally, the red cell is thought to be a spongelike stroma or frame work consisting of a mixture of proteins and lipoid substances in the meshes of which hemoglobin is held Hemoglobin is composed of 95 per cent globin (a protein), and 5 per cent heme, a porphyrin compound contain ing iron and giving color to the blood

The lipoid constituents are normally phospholipoid 58 per cent, free cholesterol 23 per cent, neutral fat 12 per cent, and cholesterol esters 7 per cent

Singly, each red corpuscle is pale yellow in color, appearing red, however, when collected in masses The red color is due, evidently, to a greater refraction caused by the large number of corpuscles in the blood

RED CELL COUNT IN MAN

The number of red corpuscles per unit volume of normal blood is of sufficient uniformity to render red cell counts of great value as diagnostic tests The mean count for human males is 5 470 000 per cu mm and for females, 4 750 000 per cu mm of blood The red cells are counted by means of an apparatus called a hemocytometer ("blood cell measurer") consisting of (1) a special pipette in which a drop of blood is diluted two hundred times with a "fixing" solution, which also destroys the white cells, (2) a counting slide, on which is a polished surface lying exactly 0 1 mm

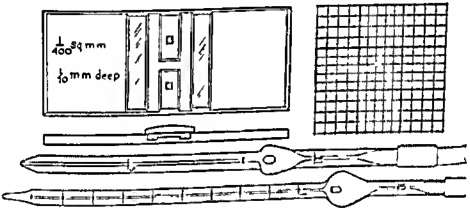


FIGURE 187

Variation in Red Cell Count in Man

Many factors control or influence the red cell count in humans. It has already been noted that sex is a factor, males having a greater number of corpuscles per unit volume than females.

Age also is a factor although not so great a one as might be expected. The following table gives the average number of corpuscles for males at different ages.

TABLE 7

Red Cell Counts of Human Males at Different Ages

Age in Years	*Number of Erythrocytes (million per cu. mm.)*
At birth	5.8
2	5.5
5	5.1
8	4.9
10	5.0
15	5.4
20	5.8
30	5.5
50	5.0
75	4.3

High altitudes also will affect the red cell count. In the process of acclimatization to the rarefied air of high altitudes (10,000 to 14,000 ft.) the increased production of erythrocytes plays an important role. As compared to an average of 5½ million cells per cu. mm. at sea level, one may find that an individual has as many as 8 million after a few weeks' residence at 14,000 ft.

Exercise causes an increased count temporarily because of the contraction of the spleen.

The red cell count also varies *in disease*. Some diseases, such as those of the respiratory tract and the heart, are associated with an increase, whereas others, such as anemia and those that produce fevers, are associated with a decrease in number.

RED CELL COUNT IN OTHER VERTEBRATES

A great difference exists between the number of red cells per unit volume in the *poikilothermic* (commonly called cold-blooded) and that in the *homoiothermic* (warm-blooded) animals (pages 422 and 423). Generally it is found that the number increases and the size of the corpuscle decreases

from the lower to the higher vertebrates The amphibians, especially, have very few cells in their blood as compared with other classes It seems as though those animals having the smallest and most numerous blood cells (1) are warm blooded, (2) are small (thus losing more body heat per volume), and (3) reside at high altitudes

In Table 8 several species with their cell counts and sizes are given The llama and goat live normally at high altitudes

TABLE 8

The Red Cell Count and Red Cell Size of Different Vertebrates

Class	*R B C* (*per cu mm*)	*Size* (*in microns*)
Pisces—Fish	140 000	23
Amphibia		
Proteus	36 000	50
Salamander	80 000	30
Frog	400 000	18
Aves—Birds	2 000 000	10
Mammalia		
Man	5 500 000	8
Horse	7 000 000	6
Llama	10 000 000	6
Goat	14 000 000	4

framework upon which hemoglobin is carried within the corpuscle Hemoglobin has a molecular weight of approximately 67,000 It consists of about 5 per cent heme, which is an iron porphyrin compound Four heme groups unite with each globin, as illustrated in the structural formula,

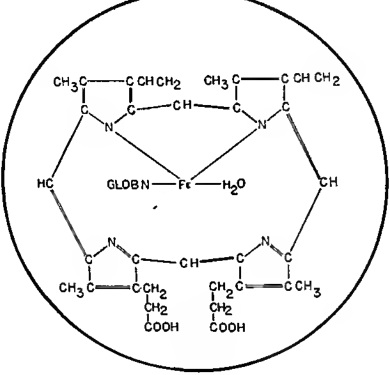


FIGURE 188

One heme molecule attached to globin

therefore, each molecule of hemoglobin contains four atoms of iron The iron is responsible for the ability of hemoglobin to combine readily with oxygen, each atom of iron combining rather loosely with one molecule of oxygen

TESTS FOR ASCERTAINING CONSTITUENTS OF BLOOD

The presence of an organic pigment, heme, found in hemoglobin can be determined by placing a drop of blood on a glass slide, adding a sodium chloride crystal and heating carefully until dry A drop of glacial acetic acid added to the residue, results in the formation of small brown rectangular crystals, which are the chloride of heme or *hemin* Heme is present in most of the red blood of vertebrates and invertebrates Obviously, hemin crystals can be produced from almost any blood by using the method

described above. The test therefore is useful only for differentiation of blood and red or brown pigments. One cannot use it for distinguishing human blood from that of a horse or a frog.

Because of the fact that the protein (globin) portions vary in different animals, hemoglobin is specific for each species; one can ascertain from the shape of the crystals produced whether the blood is that of man or some other animal. Crystals of hemoglobin may form if blood on a glass slide is treated with ammonium oxalate and allowed to dry.

The quantity of hemoglobin per unit volume of blood can be determined by several methods that are standard laboratory procedures. In the Sahli and Dare methods, a visual evaluation of the unknown blood is made by comparing it with a standard color scale. The Tallquist method is less accurate, consisting of a comparison of a blood stain with a series of color charts. The use of photoelectric colorimeters is more accurate and hence more desirable since the amount of hemoglobin is determined by the ability of a solution of hemolyzed blood to absorb light rays. The amount of light absorption is directly proportional to the amount of hemoglobin present and a direct reading may be made from the scale of the instrument. Another accurate method is one in which hemoglobin is measured by the amount of iron present. The quantity of hemoglobin varies in each individual between 12 and 17 g per 100 cc of blood

The blood of invertebrates having a circulating medium varies considerably in consistency Many species have red blood which at one time was thought to contain a substance comparable to the hemoglobin of vertebrate blood However as is discussed later (under respiration Chapter 30) the chemical nature and the properties of the invertebrate *respiratory pigments* are very different from those of vertebrate hemoglobin

Some of the members of the phylum *Mollusca* and others of the class *Crustacea* of the phylum *Arthropoda* have blood containing a pigment consisting of large molecules (molecular weight probably greater than 5 000 000) made up of many amino acids and copper which functions in a manner similar to iron in hemoglobin This substance is called *hemocyanin* and is colorless when reduced but has a blue color when oxygenated Often when oysters are brought into market during the winter months they may be partly frozen and have a definitely blue color This is owing to the lowered metabolism of the oyster which enables the hemocyanin to retain much of its oxygen since only very little of it is needed by the tissues during the period of retarded activity

THE FORMATION OF ERYTHROCYTES

Mammalian erythrocytes are cells which have lost their nuclei For this reason some believe that they are no longer living structures in the ordinary sense but merely mechanical devices Within certain bones such as the ends of the long bones (such as humerus femur and the like) ribs vertebrae sternum and portions of the skull the marrow differs from the yellow marrow found in the shafts of the long bones The marrow of the particular bones mentioned is a deep red color because of the network of small blood sinuses (*sinusoids*) lined with numerous large endothelial cells that multiply rapidly store hemoglobin within themselves lose their nuclei and take on the appearance of young red corpuscles This process of erythrocyte formation is a very important one and takes place on a large scale It has been estimated that the life span of the human erythrocyte is approximately 120 days If this is true about 200 000 000 red cells must be produced every minute

The term *erythrogenesis* (meaning red cell beginning) is applied to the development of the erythrocyte In the early embryo the liver and spleen are responsible for this development in the later embryo bone marrow also begins production and continues to do so throughout life the liver and spleen ceasing production sometime before birth However the spleen can again take up the function during periods of stress following excessive loss of blood

The cells lining the sinusoids and capillaries of the red bone marrow are called *endothelial* cells Among them are very large cells, *megaloblast* cells, which multiply rapidly to produce red blood cells They contain large nuclei and although the materials necessary for hemoglobin formation are

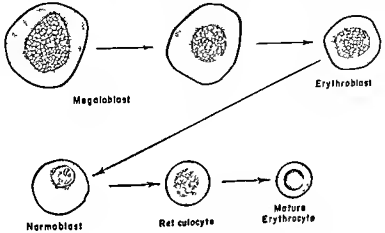


FIGURE 189

Illustrating the development of the red cell from the early megaloblast stage to the mature red cell

present, the megaloblast cells have no hemoglobin These cells divide rapidly to produce many smaller and more differentiated cells called *erythroblasts*

Erythroblasts retain their nuclei, although it is during this stage when the nuclei seem to shrink somewhat and hemoglobin begins to form The erythroblast develops into the *normoblast* in which the nuclei are still smaller At this point in development, most of the hemoglobin has been produced

The *reticulocyte* which follows is often labeled an immature erythrocyte the name being derived from the fact that a network structure seems to spread through its interior This network consists of the remnants of chromatin (see description of the cell and cell division pages 28 and 29) from the nucleus which has disintegrated and is rapidly disappearing The remainder of the hemoglobin is formed at this stage This cell is called an erythrocyte when it has lost all of its nuclear material In the normal healthy individual, the cells are released into the blood stream at some time during the reticulocyte stage

In recent years claims have been made that reticulocytes are formed from the erythroblast by a flow of protoplasm toward one end of the erythrocyte which pinches off leaving the nucleus behind It is further

claimed that mitosis could not account for more than 1 per cent of the total number of erythrocytes in the blood stream In fact, mitotic activity can be stopped entirely, yet it has been found that this has very little effect upon erythrocyte formation Further evidence must be forthcoming before these views can be fully accepted

Hemoglobin formation takes place in the nuclei of the cells during their metamorphosis It would be useless if formed outside the cell since the cell membrane is impermeable, also, hemoglobin in the plasma is rapidly destroyed and excreted Maturity of the red cell seems to depend upon the presence of hemoglobin

Iron, incorporated into the hemoglobin molecule, can be detected in the nuclei of the developing red blood cell The animal depends upon an adequate dietary supply of iron The daily requirement of the adult human is probably 5 to 15 mg It is thought that the amount of iron absorbed from the intestine depends upon the need of the body for it at a given moment Pure iron salts may fail to correct anemia resulting from iron deficiency, but it has been found that traces of copper and cobalt, as well as various other metals apparently acting as catalysts, facilitate hemoglobin formation

Since hemoglobin is such an excellent oxygen carrier one might wonder why it is not injected instead of whole blood into the circulation of those who are in need of a transfusion There are two reasons why such a procedure would not be wise (1) the liver cells would break down the hemoglobin molecule into bile pigment and globin as rapidly as they could do so, and (2) the hemoglobin molecule is small enough to pass through the pores of the blood capillaries, especially those of the kidneys and, therefore any that might have escaped the liver would pass out with the urine and feces

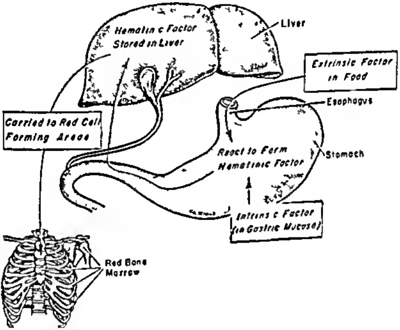
ANEMIA

Anemia is an abnormality of the blood in which there is a decrease in the quantity of hemoglobin per unit volume of blood In humans, the condition is characterized by paleness, weakness and rapid fatigue, increased heart beat, and breathlessness

If the marrow of the erythrocyte forming areas of an individual with pernicious or primary anemia, is examined microscopically, it is found that the megaloblasts, normally few in number, have become quite numerous, whereas the usually numerous normoblasts have become scarce Some factor essential for the maturation of the red cells from the megaloblast stage, is lacking in an individual suffering from pernicious anemia Thus, in this

disease, the formation of red cells cannot keep pace with their destruction, and, up until twenty one years ago, the condition was always fatal

In 1926, Dr Whipple and his associates discovered that liver was very effective in overcoming a condition of anemia in dogs, and in 1927, Minot and Murphy found that it was also efficacious in the treatment of pernicious anemia in humans It was fed in the form of partly cooked or raw liver and liver extracts Although this is not a cure for the condition, it takes the place of some factor which is essential to red cell formation Thus, today, a person suffering from this type of anemia can enjoy a normal life if liver feeding is continued



absorbed through the intestinal wall and is carried to the liver where much of it is stored. Any of it that may be necessary for immediate use is absorbed by the cells of the red bone marrow which are stimulated by this factor to continue the production of erythrocytes. Recently, Vitamin B_{12} has been identified as the important extrinsic factor. Vitamin B_{12} is, evidently, not absorbed in the alimentary tract unless it first combines with the intrinsic factor. In a person suffering from pernicious anemia, this vitamin is effective only if injected into the blood stream.

The individual suffering from pernicious anemia does not produce a sufficient quantity of the intrinsic factor in the stomach. Thus, the anti-anemic factor cannot be produced, even though there may be an abundant supply of the extrinsic factor in the diet. Consequently, the blood forming areas are not supplied and the red cell count decreases unless the antianemic factor is provided. If this is not done, death is the result.

Actually, pernicious anemia may be treated in two ways. (1) The patient may be fed beef liver or pork liver (or liver extract) in which the antianemic factor is stored. The factor can move directly to the intestine without any further action and there pass into the blood stream. (2) Sometimes desiccated hog stomach may be given. This contains the intrinsic factor which, in order to be effective, must have the extrinsic factor present in the diet at the same time. The two then react to produce the antianemic factor.

Another type of anemia is that produced by the action of toxic substances, such as lead and benzol, or by X rays or radium. These function to depress the activity of the regions forming red cells so that the normal number of cells are not produced even though a sufficient supply of antianemic factor is at hand.

Still another type is *splenic anemia* in which the spleen cells, ordinarily attacking only old red cells, now destroy young red cells also.

Secondary anemia is usually not so serious as pernicious, once the conditions producing it have been analyzed. It may occur as the result of several factors, such as: (1) a diet deficient in extrinsic factor (nutritional), (2) a diet deficient in iron (nutritional), and (3) hemorrhages, especially those of a slow, but prolonged type. Proper treatment for these conditions is obvious. For extrinsic factor deficiency, a suitable diet is prescribed. For iron deficiency, ferrous carbonate or sulfate, along with minute quantities of copper and cobalt, is given. For anemia caused by hemorrhage, the same dietary factors are needed with the addition of rest. In severe cases, one must resort to transfusion.

ADDITIONAL READING

Gradwohl, R B H, *Clinical Laboratory Methods and Diagnosis*, 4th ed (St Louis Mosby, 1948), vol I, ch 4 Procedures for examination of blood cells

Haden, R L, *Principles of Hematology* (Philadelphia Lea and Febiger, 1940) Blood examination

22

Blood Volume and Problems in Transfusion

CHANGES IN BLOOD VOLUME

Under normal conditions, the blood volume tends to remain constant. Fluid that may have a tendency to collect in the blood stream soon passes out by way of the excretory organs—the kidneys, skin, and lungs. Sometimes however, this equilibrium is disrupted and, as a result, the blood volume may show a decrease under some conditions, or an increase under others.

An increase in the volume of the blood may be established in two ways: (1) by constriction of the spleen and other blood reservoirs, and (2) by diffusion of water from tissue fluid into the blood.

An *increase in blood volume*, evidently caused both by constriction of the spleen and by water diffusion from the tissues, occurs when environmental temperatures are high. However, increase in blood volume during exercise or emotional excitement appears to be the result only of the constriction of the spleen.

A *decrease in the volume* of the blood may be brought about by (1) hemorrhage, (2) decrease in red cell formation (anemia), (3) traumatic shock (loss of plasma), and (4) loss of blood water (*anhydremia*).

THE EFFECTS OF HEMORRHAGE

Naturally, the effects of hemorrhage on the body depend upon the amount of blood lost. If the loss is more than 30 to 35 per cent of the total blood volume, the body cannot compensate for this decrease rapidly enough and the person affected may die unless transfusion is undertaken. If less than this amount is lost, a healthy individual usually can compensate for it by the action of certain adjustive mechanisms in the body that are brought into play immediately. The blood volume may then be returned to normal in a relatively short period of time by the diffusion of tissue fluid into the blood. However, this results in a dilution of the blood so that the number of erythrocytes per unit volume is reduced. Thus a much longer time is required for the red blood cell count to be restored to normal. For

example, if 500 cc of blood are lost, the volume is restored in about one hour, whereas it takes several weeks for the red blood cells to be replaced The mechanisms that aid in restoration of blood loss include (1) a decrease in the capacity of the circulatory system by vasoconstriction, (2) a constriction of the spleen, (3) the diffusion of tissue fluids into the vessels, and (4) a more rapid formation of red cells

REPLACEMENT OF LOST BLOOD

Today, transfusions are an almost commonplace method of replacing lost blood The advances in our knowledge concerning proper procedure for transfusions, made since World War I, have been phenomenal This knowledge has been directly responsible for saving innumerable lives However, it has not been so very long (the early part of this century) since attempted treatment by transfusion was always hazardous and, in many cases, fatal

Because of the rapid coagulation of blood when it comes in contact with foreign objects, some of the very early attempts at restoration of lost blood depended upon defibrination (the removal of fibrin to prevent coagulation), which consists of whipping the blood with broom straws or the like during the clotting process The fibrin collects on the straws and the excess thrombin remains in the fluid Hence, blood obtained by this method always contains *thrombin* Since thrombin is directly responsible for the formation of fibrin (the clot), it is obvious that this blood if injected into the circulatory system of an individual might produce sufficient clotting in the vessels to be immediately fatal When it was finally realized that this method was always hazardous (as was the earlier method of transfusing into man, the blood of other animals such as the dog or horse) it was discontinued in favor of a more direct method This consisted of bringing a vein (opened and cannulated) of the recipient into direct communication with a vein of the donor During World War I it was found that by coating needles syringes, and containers with paraffin or oil, clotting occurred much more slowly We know now that any surface that the blood does not wet (that is cling to readily) is not conducive to disintegration of blood platelets which process as we shall see may initiate the process of blood clotting However, other hazards became evident for example, this method proved to be an excellent way to transmit diseases to either recipient or donor

In many cases the blood loss is not so great that whole blood transfusion is necessary *Physiological saline solutions* can be injected, especially if the lowered blood volume is due chiefly to a dehydration or loss of blood water

Gum solutions were used with evident success during World War I A 6 per cent solution of *gum acacia* proved to be especially beneficial since it simulated the viscosity as well as the osmotic concentration of blood plasma Also the molecules of gum acacia do not escape through the capillary membrane so readily as do those of saline solutions

In World War II patients receiving transfusions at the front, where whole blood transfusion was virtually impossible, were injected with *dried plasma* dissolved in sterile water This was a great step forward, especially for those whose injuries were so severe that they could not be moved without emergency treatment

Whole blood transfusion is, or course the most desirable treatment for serious cases and whenever possible it should be used for conditions such as severe hemorrhage and wound shock The red cells of transfused blood survive and, since their average life may be as long as that of the red cells of the recipient s blood carry out their functions for many days

METHODS FOR PRESERVING BLOOD

There are many methods of preserving blood in the fluid state Some of these are (1) by defibrination or whipping which has already been mentioned (2) by cooling to 0 degrees C which retards clotting and preserves the platelets (3) by removing calcium ions by adding sodium citrate (calcium citrate does not dissociate sufficiently into ions) or sodium oxalate which precipitates the calcium, (4) by preserving the blood in vessels the surfaces of which it does not wet, such as beakers coated with paraffin, (5) by the addition of heparin which is an antiprothrombin and thus prevents the process of coagulation (6) by the addition of hirudin produced by leeches or similar substances that prevent clotting and (7) by the addition of a suitable concentration of salts such as magnesium sulfate Only a few of these methods can be used for preserving blood to be used for transfusion Blood preserved by cooling by coating the container, or by removal of calcium ions is most satisfactory, at least it is more satisfactory than that preserved by the other methods mentioned here Blood obtained by methods number (1) and (7) could not be used for transfusion

BLOOD GROUPS

Although the classification of blood groups is comparatively new to science, it was realized even before the early days of the direct-communication method of blood transfusion that the blood of one human was not always

compatible with that of another. Upon examination, it was soon discovered that incompatible bloods when mixed always resulted in agglutination or clumping of the erythrocytes. This is dangerous in transfusion, especially if the agglutination is pronounced, the clumps of corpuscles will cause blockage in the smaller blood vessels after which they may hemolyze and cause the formation of a clot. This same reaction follows the mixing of blood from one species of animal with that of another.

As a result of the work of several investigators in the first few years of this century (notably that of Landsteiner, Jansky, and Moss), it was established that the blood of humans can be classified as falling into one of four main groups, according to its agglutinating reaction.

It has been found that there are in human plasma substances known as *agglutinins* with the ability to act on the red cells of other individuals and cause them to clump. The red cells, in order to be susceptible to the effect of the agglutinins, must contain *agglutinogens* which are acted upon by the agglutinins.

Two agglutinogens and two agglutinins have been postulated. The two agglutinogens are referred to as A and B. Thus, in humans there are four types of blood: in one we find erythrocytes with A type agglutinogen, in another, B type, another, both A and B, and still another with neither type. The blood is classified as falling into one of these four groups (Table 9). The two types of agglutinins have been labeled, alpha (α) and beta (β).

TABLE 9

Classification of Blood Groups

DESIGNATION OF GROUPS				
Jansky	*Moss*	*Landsteiner (International)*	*Agglutinogen in the Cells*	*Agglutinin in the Serum*
I	IV	O	—	α and β
II	II	A	A	β
III	III	B	B	α
IV	I	AB	A and B	—

These react with A and B agglutinogens respectively. Therefore, individuals with A agglutinogens in their red cells could not have alpha agglutinins in their plasma. These two components are incompatible and cannot remain together in the same blood. It is obvious, then, that individuals with A type blood must have beta agglutinins in their plasma. Likewise, individuals with corpuscles containing B agglutinogens, must have alpha

agglutinins in their plasma one with A and B agglutinogens could have neither alpha nor beta since the former is incompatible with A and the latter with B and one with O agglutinogens contains both alpha and beta in the plasma since it has been shown by tests that serum from O blood causes agglutination of all other types of corpuscles

At present the international designation is used almost universally The earlier classifications of Jansky and Moss which differed in their types I and IV aroused much confusion The international is superior to the others in that we know the type of agglutinogen (and agglutinin) present by the symbols

The student should keep in mind the fact that in blood transfusions the quantity of blood donated is usually small compared to the volume of the recipient s blood Therefore although *the cells of the donated blood are exposed to the full effect of the agglutinins in the recipient s plasma the recipient s cells are not affected greatly by the donor s plasma* Normally the donor s plasma is diluted so rapidly in the blood stream of the recipient that it does not affect the erythrocytes of the recipient In some cases if the transfusion is given too fast the donor s blood is not greatly diluted at once and thus some of the recipient s cells may be agglutinated Another factor to be considered is the original concentration of agglutinin in the donor s plasma If this is too great then the dilution will be less and thus the agglutinin may act on the recipient s cells

The erythrocytes of persons with type O blood are not agglutinated by contact with the plasma of any other type They do not have any agglutinogens in them and therefore the agglutinins of the other types cannot act on these cells For this reason such persons are called *universal donors* But the plasma of the O type blood has both alpha and beta agglutinins in it If the transfusion is not given too rapidly and if the agglutinins are not in too great a concentration they will not cause clumping of the recipient s erythrocytes However the safest procedure would be to give to the recipient the same type of blood as his own

Persons with type AB blood have at times been referred to as *universal recipients* because they may accept for transfusion blood from any of the other groups as well as their own This is possible because there are no agglutinins in AB blood and the recipient s corpuscles are not acted upon since the donor s plasma is diluted too greatly during transfusion to be effective However the term universal recipient is dangerously misleading For example if the donor belongs to group O the recipient s (AB) cells have a double chance of becoming agglutinated since both agglutinins are present in O type blood

METHOD FOR DETERMINING BLOOD GROUPS

The method used for determining blood groups is rather simple and is best described in the accompanying figure Blood sera * from A type

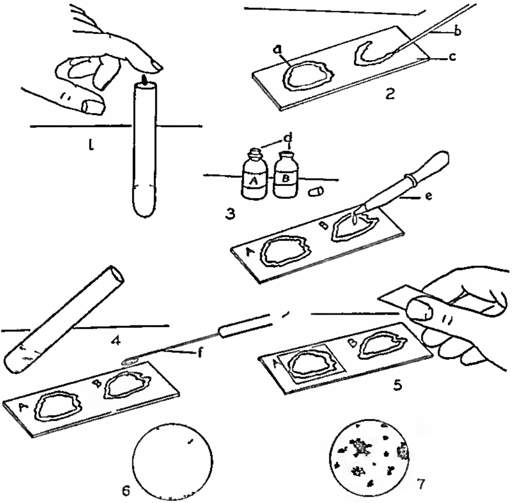
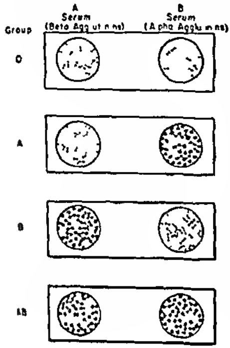


FIGURE 101

and B type bloods are obtained and a drop of each added to a glass slide. The unknown blood specimen to be tested is diluted as suggested and a small drop added to each of the drops of sera. If the corpuscles are not agglutinated by either sera, the unknown belongs to group O; if they are agglutinated by the A serum but not the B, it belongs to group B; if they are agglutinated by B but not A, it belongs to group A; and if they are agglutinated by both sera, it belongs to group AB.



The agglutination may be seen with the naked eye if the drops of sera and corpuscles are large enough; otherwise it can be detected with the aid of a microscope. The clumping usually occurs within a few minutes, but sometimes the reaction may take 15 to 20 min.

in the other The manner in which groups may be inherited is illustrated in Figure 193 in which a person with group B(BO) blood is crossed with one of group O The offspring will be half recessive, or O type, and half mixed B type

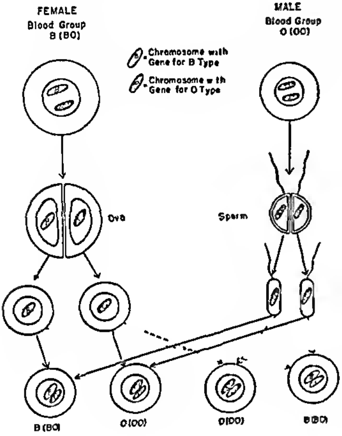


FIGURE 193

Illustrating the inheritance of blood groups in man A mixed B(BO) type crossed with an O type results in offspring half of which are mixed B(BO) and the other half O

LEGAL ASPECTS OF BLOOD GROUPING

Information gained on the subject of blood grouping may be used in investigations of disputed paternity. However, one can only prove that a particular suspect is *not* the father of the child, never that he is the father.

The child receives one of the three possible blood group genes from each parent. A parent with O type blood can supply only a gene for O type; a parent with A blood may supply either A genes or O genes; one with B blood may supply either B or O genes; and one with AB blood may supply either A or B. The possible combinations are presented in Table 11.

TABLE 11

Inherited Combination of Blood Groups

Child's Blood Group	*Parents Gave It—*	*If Mother's Blood Is—*	*Father's Blood Could Not Have Been—*
O	O × O	O, A, or B (could not have been AB)	AB
A	A × A or A × O	B (would have to be BO) or O	B or O
B	B × B or B × O	A (would have to be AO) or O	A or O
AB	A × B	A, B, or AB (could not have been O)	O

HEMOLYSIS

The phenomenon known as hemolysis is the freeing of hemoglobin by the disintegration of the red blood cells.

It has been pointed out that if whole blood is mixed with distilled water there is considerable change in osmotic pressure. Water flows into the blood cells, causing them to swell until they burst and lose their hemoglobin. This is called *hemolysis*.

There are many means by which hemolysis may be induced, and a few of them will be considered in some detail.

1. *Hypotonic solutions* are very effective. The erythrocyte contains materials that cannot pass out of the cell, but, on the other hand, plasma has materials that cannot pass in. In normal blood the plasma and corpuscles are in osmotic equilibrium; that is, the plasma is isotonic with the contents of the erythrocyte. Thus, if the plasma is diluted with distilled water, the

latter passes through the erythrocyte membrane as described above There is a certain amount of resistance shown by the erythrocyte to the diffusion pressure produced by this method The normal concentration of substances in human blood plasma is equal to about 0 94 per cent sodium chloride (NaCl) Therefore, any concentration below this becomes hypotonic to the erythrocytes which gradually become more and more swollen as this concentration decreases but they do not burst (hemolyze) until the concentration of substances in the outer medium decreases to a value equal to about 0 4 per cent sodium chloride or less

The permeability of the erythrocyte membrane is quite different from that of the membrane of the blood capillaries We have seen that most of the crystalloids and small organic molecules, and even some proteins, including hemoglobin, will move through the capillary wall The erythrocyte membrane, however, is quite selective' of the substances that are allowed to pass through it It is impermeable to plasma proteins, hemoglobin, and to sodium, potassium, calcium, and magnesium ions (Na^+, K^+, Ca^{++}, and Mg^{++}) It allows water to flow back and forth freely as well as the bicarbonate, chloride, and hydroxyl anions (HCO_3^-, Cl^-, OH^-) the cation, hydrogen (H^+), and organic substances such as urea amino acids and uric acid

Hypertonic solutions for human blood are those which have concentrations equal to or above that of 0 94 per cent sodium chloride They have the opposite effect of hypotonic solutions and cause *crenation* of the corpuscles as illustrated in Figure 194

FIGURE 194

The effects of hypotonic and hypertonic solutions on red blood cells The hypotonic solution results in swelling and hemolysis while the hypertonic solution causes crenation of the corpuscles

3 *Snake and spider venoms* and the poisons of some insects evidently destroy the cell membrane by their action on the lecithin molecule and in this way the hemoglobin is allowed to escape

4 *Bacterial* toxins may exert a powerful hemolytic action on the blood cells Toxic substances produced by bacteria may have a direct effect on the red cells and destroy them The *malarial parasite*, a protozoan cell residing in the erythrocytes during part of its life cycle, causes their destruction In some cases, the hemolysis produced by these parasites is so great that the liver cells cannot take up the escaped hemoglobin rapidly enough The hemoglobin then passes into the urine which becomes dark brown to almost black, the condition is sometimes referred to as blackwater fever The appearance of hemoglobin in the urine is called *hemoglobinuria*

5 *Specific hemolysins* are produced in animals when the blood corpuscles of a foreign species are injected into the blood stream This reaction is similar to immunological reactions of the body against bacterial invasion This applies also to the blood streams of animals of the same species whose bloods are incompatible For example, if a small quantity of red cells from the blood of a person belonging to group A are injected into the veins of one belonging to group B, the red cells clump or agglutinate Since only a few are injected, no great damage is done Hemolysis follows agglutination as a secondary effect However, if a series of injections is made in the manner just described, over a period of several days, it has been found that antibody like substances develop in the plasma causing hemolysis of the injected corpuscles immediately, before they have time to agglutinate The substance produced in the plasma is called a *specific hemolysin* because it is specific only for those particular erythrocytes

Rh FACTOR AND ERYTHROBLASTOSIS

In recent years, many articles have appeared in newspapers and popular magazines, as well as in scientific journals, concerning the Rh factor Nothing was known about it until 1940, when two investigators (Landsteiner and Wiener) injected blood from rhesus monkeys into the blood stream of rabbits These scientists found that the antibodies (page 320), produced in the rabbit blood in response to the injection, caused agglutination of the erythrocytes of the blood of rhesus monkeys The serum or plasma was said to have produced an antirhesus factor On the other hand, the erythrocytes from the monkey were said to possess the *rhesus* or *Rh* factor This action, of course, was to be expected from our knowledge of processes of immunization However, it was discovered that when the erythrocytes from human blood were added to the antirhesus serum, agglutination occurred in 85 per cent of the individuals of the white race, in 95 5 per cent of

Negroes, and in about 98 per cent of Japanese and Chinese In other words the erythrocytes of these individuals contained the same substance as the erythrocytes of the rhesus monkey, ***the Rh factor*** These individuals are said to be Rh positive, while the remaining 15 per cent of the white race, 45 per cent of Negroes, and 2 per cent of Chinese and Japanese are Rh negative, their erythrocytes are not agglutinated by the treated rabbit serum because they do not have the agglutinable factor in their blood

These factors are inherited and follow the Mendelian Law The Rh positive (Rh^{+}) factor is dominant, the Rh negative (Rh^{-} or rh) factor is recessive Therefore, if both should be present in the chromosomes of the cells of humans, the dominant factor would stand out Thus, the offspring of an Rh negative mother and a *pure* Rh positive father are all Rh positive (Figure 195)

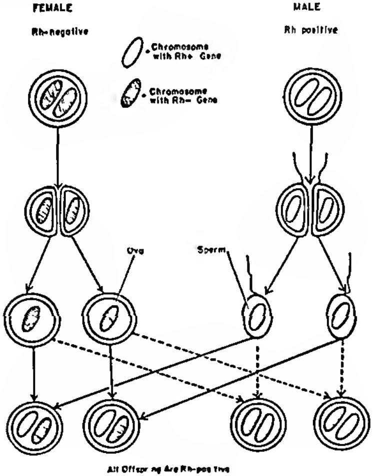


FIGURE 195

The inheritance of Rh factor in offspring of an Rh negative mother and an Rh positive father

The discovery of the existence of an Rh factor led to an understanding of at least two problems that had baffled physicians and physiologists for many years One was the fact that although the majority of blood transfusions were successful when blood of the same group as the recipient was donated occasionally serious mishaps occurred It is now obvious that the bloods of two persons belonging to the same blood group are compatible only if they are both Rh positive or both Rh negative The effects of mixing the bloods of two individuals one Rh positive and the other Rh negative are most serious if a second or third transfusion is made If the blood of an Rh positive individual is transfused into that of an Rh negative individual antibodies for Rh positive erythrocytes are formed and released into the plasma of the Rh negative blood These antibodies agglutinate and hemolyze the erythrocytes of the Rh positive individual The agglutinins remain and have much greater effect if a second and a still greater effect if a third transfusion is made

The other condition that puzzled physicians was that known as *erythroblastosis fetalis* which is a hemolytic reaction of the unborn or newborn child It is characterized by jaundice edema and anemia and is frequently fatal Before our present understanding of the Rh problem was reached the cause of this condition was not known

We now know that the condition may appear in the children of an Rh negative mother and an Rh positive father although its appearance is not as frequent as might be expected It is claimed that the combination of an Rh negative mother and an Rh positive child (Figure 195) occurs in one in every ten pregnancies although only one pregnancy in about 400 results in erythroblastosis

The appearance of erythroblastosis is subject to the following sequence of events

1 Rh agglutinogens (antigens) found in the erythrocytes from an Rh positive fetus pass into the blood stream of the Rh negative mother This can happen only if some defect or break occurs in the placental circulation so that erythrocytes of the fetus can pass through into the mother s blood stream

2 In the tissues of the Rh negative mother the Rh positive agglutinogens in the erythrocytes initiate the formation of antibodies or agglutinins (immunizing reaction) which are released into the blood stream and cause agglutination and hemolysis of the Rh positive erythrocytes

3 The agglutinins converse to the action of agglutinogens can pass through the placental membranes and thus they soon diffuse into the Rh positive blood of the fetus

4 Here they react with the Rh positive erythrocytes and produce the hemolytic reaction of the unborn or newborn child

Today most of these children may be saved by immediately transfusing Rh negative blood (which has not been sensitized to Rh positive) into their circulatory systems Rh positive blood cannot be used for this transfusion since the agglutinins already present in the infant's blood would destroy it as rapidly as it entered

ADDITIONAL READING

Gradwohl, R B H, *Clinical Laboratory Methods and Diagnosis*, 4th ed (St Louis Mosby 1948) vol I, ch 5 Techniques in blood typing

Schiff, F, and W C Boyd, *Blood Grouping Technique* (New York Interscience, 1942) Details of blood typing technique and applications

23

The Spleen, Leucocytes, Blood Coagulation

THE SPLEEN AND ITS FUNCTIONS

THE SPLEEN lies just beneath the stomach on the left side of the body It i well supplied with large colorless cells responsible for the destruction of the old worn out erythrocytes It has a very rich supply of blood carried, by arteries that empty for the most part directly into the spaces or sinuses comprising the greater part of the spleen The blood then collects in veins leading from the spaces and is carried back to the general circulation

The spleen has four recognized functions (1) It is a reservoir for erythrocytes stored in the spleen until such a time as they are needed (2) It is sometimes referred to as the graveyard of the red cells because of their destruction by the large colorless cells of the spleen (3) It produces lymphocytes (4) It has a temporary role in the fetus in the formation of erythrocytes

THE SPLEEN AS A RESERVOIR FOR ERYTHROCYTES

The English physiologist Barcroft when he and his party were traveling to the Peruvian Andes for the purpose of making studies on acclimatization to high altitudes accidentally discovered that the spleen is a reservoir for erythrocytes During the voyage many blood tests were made upon the various members of the expedition They noted that as they neared the tropics the blood volume and hemoglobin concentration of each individual increased but after they again reached more temperate regions the blood volume and hemoglobin returned to normal Barcroft concluded that the increase in volume was owing to an increase in number of red cells which had been released by some (at the time unknown) reservoir in the circulatory system The spleen was of course suspected and subsequent investigations have borne out the correctness of these suspicions

The contraction of the spleen is evidently initiated by sympathetic stimulation The organ contains about 5 per cent of the total blood supply which during periods of stress is made available to the mammalian body by contraction The smooth muscles contract forcing the concentrated

red cells out of the splenic sinuses or cavities This also occurs when the temperature is increased (as mentioned earlier) and during lowered blood pressure, exercise, and anoxia (oxygen deficiency in tissues) In other

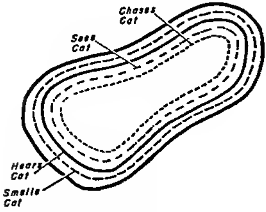


FIGURE 196

Constriction of dog spleen

words the spleen of mammals functions in this manner during emergencies of the sort mentioned

ERYTHROCYTE DESTRUCTION IN THE SPLEEN

The large colorless cells called macrophages, which line the cavities or sinuses of the spleen are amoeboid in their movement, and have a part in the removal of disintegrated erythrocytes from the blood stream When they ingest and digest broken down red cells these macrophages selectively take up iron and globin from the hemoglobin, most of which can be used again by the cells of the blood forming regions The remaining portion of the hemoglobin molecule, hematin minus iron, is released into the blood stream and it is excreted from the body as bile pigment by way of the liver and gall bladder

THE RETICULO ENDOTHELIAL SYSTEM

There are two general types of *phagocytes* (eating cells) in the body, the microphages (small eaters) and the macrophages (large eaters) which comprise the reticulo endothelial system Their differences were first noted by Metschnikoff (1887) who was also the first to emphasize the importance of leucocytes as body defenders against the inroads of disease-producing bacteria

The *microphages* include the leucocytes of the circulating blood whereas the *macrophages* much larger than the microphages having long oval nuclei occur chiefly in other tissues The macrophages are especially abundant in connective tissue, liver, spleen lymph nodes and bone marrow

they line the blood capillaries where they form a network, or reticulum. All of these large colorless cells form a part of the *reticulo endothelial system*. The macrophage cells evidently carry on several functions. (1) In the liver and spleen they engulf and destroy old worn out erythrocytes as already noted. (2) Others take care of any particulate matter that they contact in the blood stream. (3) They may become motile and play a very active role in the repair of tissues. (4) They have a great deal to do with the mechanism of immunization.

THE COLORLESS CORPUSCLES OR LEUCOCYTES

The term *leucocyte* means white cell and includes all the colorless or white corpuscles in the body. Cells similar to the leucocytes of our blood stream are found throughout the animal kingdom. Even sponges have wandering cells that move about in an amoeboid fashion as do those of other small invertebrate species. The functions of these cells in the lower forms vary—some of them are excretory, some bring food into the system of an organism, others are concerned with regeneration, tissue repair, and immunization processes. In the human body they are far less numerous than erythrocytes but, nevertheless, play a very important part in maintaining normal bodily function. There are, on the average, about 6000 to 10 000 leucocytes per cubic millimeter of blood in the normal individual. This figure may increase tenfold or more under certain pathological conditions. They increase also during exercise, sometimes up to 35 000 per cubic millimeter. The length of life of the leucocyte is not known, but has been calculated to be as great as twenty one days.

When viewed under the high power of the microscope, they appear as small, nucleated cells that exhibit an amoeboid type of movement. Sometimes if leucocytes are examined in capillaries near the surface, they may be seen migrating through the capillary wall. Evidently, they force their way through the capillary wall at points where the cells making up the wall come in contact with one another. This is called *diapedesis*. In this manner

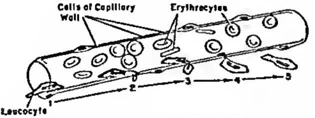


FIGURE 197

Diapedesis or the movement of leucocytes from the capillary into the tissue spaces. 1, 2, 3, 4 and 5—successive movements of leucocytes through the capillary wall.

they get out into the tissues and make their way to an infected area where they can attack the bacteria, thus, perhaps, warding off deeper infections.

CLASSIFICATION OF THE LEUCOCYTES

The colorless corpuscles or leucocytes may be classified as follows:

1 Polymorphonuclear
  - a Neutrophils
  - b Eosinophils
  - c Basophils

2 Lymphocytes

3 Monocytes

Sometimes the polymorphs are grouped together as *granulocytes* and the lymphocytes and monocytes, as *agranulocytes*

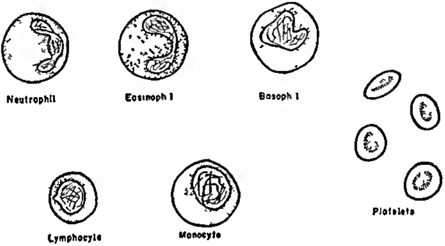


FIGURE 198

Sketches of different types of leucocytes and platelets

All of the polymorphs are produced in the red bone marrow They make up 68 to 75 per cent of the leucocytes, by far the greater number of these being the *neutrophils* which constitute 64 to 70 per cent of the total leucocyte count The neutrophils have been given their name because of their rather small cytoplasmic granules, which are not stained by either basic or acidic stains, but by neutral stains, such as neutral red Neutrophils are about 10 to 15 microns in diameter when assuming a spherical shape and their nuclei are two-, three-, or four lobed These leucocytes play a highly important role as defenders of the body against bacteria Pus is made up chiefly of living and dead neutrophils along with other debris

The *eosinophils* constitute only about 3 to 4 per cent of the total count They resemble the neutrophils except that their granules are large and will stain with an acid dye, such as eosin They are also 10 to 15 microns in diameter and their nuclei are almost always bilobed An increase of

eosinophils occurs in certain diseases such as various bronchial and skin infections parasitism and asthma The manner in which they function is rather obscure

Approximately ½ to 1 per cent of the leucocytes are *basophils* which are about the same size as the other polymorphs they also have lobed nuclei and the coarse granules are stained by basic dyes

The *lymphocytes* are formed in the lymphoid tissue found in the lymph nodes spleen adenoids and tonsils They are the smallest of the colorless blood cells their function is still unknown They do not ingest particulate matter or bacteria as do other leucocytes It has been suggested that they may aid in tissue repair and in fat absorption perhaps they play a role in the formation of antibodies They seem to accumulate in tissues in great numbers during later stages of inflammation they also collect around cancerous lesions and other degenerative tissue Their length of life may be very short it has been suggested to be as less than twenty four hours

Monocytes are sometimes referred to as mast cells They are wandering cells somewhat similar to the macrophage cells of the reticulo endothelial tissue and probably arise from them Monocytes are phagocytic in that they will engulf bacteria but they take up other particulate materials as well also they may produce proteolytic enzymes

Any increase in the number of colorless corpuscles above 10 000 per cubic millimeter is called *leucocytosis* and as mentioned previously this condition occurs during exercise in infections where the leucocytes sometimes number over 100 000 per cubic millimeter during pregnancy and following a hemorrhage *Leukemia* (sometimes called cancer of the blood) is a condition in which the number of leucocytes may rise to as high as 250 000 per cubic millimeter with many immature cells also found in the blood stream Anemia is associated with this condition

Any decrease of these corpuscles below the normal minimal number of 5 000 per cubic millimeter is called *leucopenia* In some cases the count may become so dangerously low that the body is unable to defend itself Poor nutrition diabetes influenza and certain drugs may bring about this condition

THE DEFENSIVE MECHANISM OF THE BLOOD

The blood has several mechanisms for defending the body against invading organisms Very few microorganisms can penetrate the normal epithelium and mucous membranes lining the alimentary tract nasal cavity and respiratory structures For that reason these tissues are called the *first line of defense* against infection

processes may take five to eight days or more before their products can outweigh the effects of the toxins. This period during which the balance is finally weighted in favor of the antibodies is often called the crisis.

Any foreign proteins that may get into the blood stream are referred to as antigens since they cause the reticulo endothelial cells to produce antibodies which prevent further action of the antigen. The antibodies produced by the action of any antigen on the reticulo endothelial cells are specific for that antigen only. Therefore, we must inoculate or vaccinate against each specific disease, no vaccine will immunize against any disease entity except the one for which it was produced.

Today many of the most deadly diseases of mankind have been conquered by artificially immunizing persons against these diseases. This may be done by actually injecting a small quantity of antigen or toxin (the bacteria having been killed) which stimulates the reticulo endothelial cells to produce antibodies which counteract the effect of the disease. As a result the danger of infection is greatly minimized or completely removed.

Sometimes a person contracts a disease such as diphtheria before he can be inoculated against it. Then the physician injects antitoxin (antibodies) already preformed in horse serum. The antitoxin is produced by injecting the horse with toxins which stimulate the formation of antitoxin. Some of the blood of the horse is then drawn off, the serum is removed and used for inoculation. For some diseases immunity is more lasting than for others. This type of treatment and immunization (especially of children) has reduced the fatalities from diphtheria from 50 per cent, in the years before such treatment was known, to about 2 per cent at the present time.

BLOOD PLATELETS

The blood platelets or *thrombocytes* are the smallest corpuscles in the blood, measuring 2 to 3 microns in diameter. They are round or oval disc-shaped cells without nuclei but containing granules. They form as fragments from the large multinucleated cells, *megakaryocytes*, of the red bone marrow. There are about 250 000 to 400 000 platelets per cubic millimeter of blood.

Their outstanding characteristic is the rapidity with which they disintegrate once they come in contact with a foreign surface. Within a few seconds after blood is shed the platelets clump together or agglutinate and then break up, releasing their contents to the plasma. The clumping of the platelets may be a means of blocking the outflow of blood when small arterioles or venules are injured. At any rate it is comparable to the manner

in which body fluids are protected from loss in many of the lower animals by the thrombocytes in their circulatory systems

Thromboplastin or *cephalin* is one of the constituents of the blood platelets which initiates the process of coagulation or clotting This substance is also present in other tissue cells and is released when the tissues are cut or lacerated Therefore, if blood is drawn carefully into clean containers so that it does not come in contact with the tissue cells and if the blood platelets do not disintegrate immediately (for example by oiling surface of container), coagulation will take place very slowly The role of blood platelets in clotting is further confirmed upon observing the blood of birds or fishes having no blood platelets If the blood from these animals is carefully drawn into a beaker or other container so that it does not contact the injured tissue cells it does not coagulate It can be made to coagulate however, if it is brought into contact with injured tissue cells or if some blood platelets are put into it

If freshly drawn blood on a glass slide is observed under the microscope it is found that the clotting is due to the formation of fine threadlike structures running in all directions and becoming a network in which most of the formed elements (blood cells) are enmeshed The erythrocytes and leucocytes have no active function in the clotting, it is a process dependent chiefly on substances found in the plasma However, these cells do add to the bulk of the clot that is formed

The microscopic threads are made up of a substance called *fibrin*, an insoluble protein produced by the action of two other substances, *fibrinogen* a soluble plasma protein and *thrombin*, also a protein, appearing in the plasma only after the coagulation process has begun The fibrin threads are the materials that are removed when blood is whipped with broom straws to which the threads adhere

Thrombin does not exist normally in the circulating blood, it, therefore must have a precursor that is soluble and does not interfere with the usual flow of the blood Such a precursor, called *prothrombin*, has been found in the plasma Prothrombin is changed to thrombin in the presence of calcium and *thromboplastin*

COAGULATION TIME

The rate of coagulation varies considerably in different individuals there being many factors affecting clotting time Therefore, these factors must be controlled if comparable results are to be obtained in research concerned with this phenomenon The most important of these factors are (1) *Temperature* the increase of which causes a decrease in clotting time if the blood is kept at a low temperature, 0 degrees C, clotting is delayed for days (2) *Agitation* of the blood hastens clotting careful handling prolongs it (3) *Unclean apparatus* used for obtaining and storing the blood results in more rapid destruction of the platelets and hence more rapid coagulation (4) *Increase in calcium ion content* of the blood decreases clotting time whereas the addition of sodium (or potassium) citrate or oxalate prevents it (5) The *method for obtaining blood* is important as is the manner in which it is obtained Blood drawn directly from a vein does not clot so rapidly as blood obtained by a skin puncture In case of a skin puncture, thromboplastin is released from the tissue cells and gets into the blood as it flows by

There is a bleeding disease or condition occurring in cattle, occasionally, in which the blood clots slowly or fails to clot at all The condition is produced when the cattle feed upon spoiled sweet clover in which there is a toxic substance called *dicoumarin* This substance acts to prevent the pro-

duction of *prothrombin*, an important clotting element, in the liver The action of dicoumarin appears to be just the reverse of the action of vitamin K which stimulates prothrombin formation A synthetic substance, called dicoumarol, which has an action similar to dicoumarin, is sometimes used orally in human cases of threatened *thrombosis*, or clotting within the blood vessels, in order to lower the prothrombin level of the plasma which in creases the clotting time Too much dicoumarol in the system may be dangerous and, in cases of over dosage, since its action is not antagonized by vitamin K or any other known substance, the only recourse is blood trans fusion

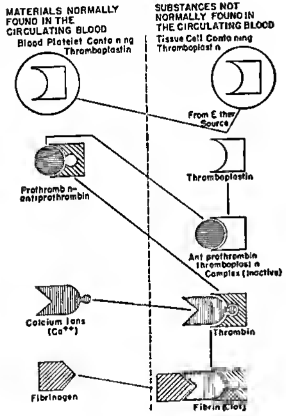


FIGURE 201

Howell's theory of blood clotting The symbols represent the various reacting substances in blood and tissue

THEORIES OF BLOOD COAGULATION

According to the theory of blood coagulation set forth by Howell, there is present in blood a substance that normally prevents prothrombin from uniting with calcium to form thrombin This substance he called *antipro thrombin* *Heparin* a material present in liver and other tissues has an action similar to antiprothrombin, but is probably not the normal anticoagu lant of the blood It has been thought that it may function as a local anti

coagulant in small blood vessels, for example. Thromboplastin has a great affinity for antiprothrombin and removes it from the field of action. Therefore, in order that blood may clot, thromboplastin must be released from the tissue cells or blood platelets. This, in turn, frees prothrombin which acts with calcium to produce thrombin. The sequence of events is represented in the accompanying figure.

In the postulation of any theory of blood coagulation the presence of certain soluble substances normally in the blood is taken into consideration. These substances are calcium ions, prothrombin and fibrinogen. The soluble thromboplastin or thrombin make their appearance after the platelets disintegrate or after the tissue cells are ruptured.

THROMBOSIS (INTRAVASCULAR CLOTTING) AND EMBOLISM

The formation of a blood clot in a blood vessel, partially or completely closing that vessel, is called *thrombosis;* and the clot itself is called a *thrombus.* The blood is protected against this intravascular clotting by the presence of antiprothrombin and the absence of thromboplastin in the plasma. There are many times, however, during life, when injuries are suffered that involve the crushing of blood vessels. This releases some thromboplastin, thus causing a clot, or thrombus, to form. This activity is perhaps local for the most part, since the thromboplastin is not concentrated enough to exert its influence at some distant point in the circulatory system.

Sometimes a thrombus or a part of it breaks away and is carried by the blood stream to some other part of the circulatory system. It is now referred to as an *embolus,* and the condition as embolism. The portion of the body in which an embolus lodges determines how serious its effects may become. If it arises from a thrombus produced in the veins, it may be carried to the right side of the heart (see circulation, page 335) and from there by way of the pulmonary arteries to the lungs and may interfere with proper gaseous exchange; if it should be formed in the pulmonary veins or the left side of the heart, it could obstruct the coronaries or it could be carried to the brain and interfere with the normal functioning of some vital center or centers.

DEFECTIVE CLOTTING OF THE BLOOD

There are several conditions found in man which cause defective clotting of the blood; that is, the blood either coagulates slowly or not at all. One such type of bleeding that may be found in both males and females is due to a deficiency of vitamin K in the blood stream. Vitamin K is essential for prothrombin formation, but sometimes it is not absorbed through the intestinal wall. This is sometimes owing to the absence of bile salts which

are necessary for absorption of lipoids, vitamin K, as formed naturally, is a lipoid In cases of bile deficiency, water soluble forms of vitamin K may be added to the diet, or bile salts may be ingested along with the natural vitamins, or vitamin K may be injected into the blood stream Vitamin K stimulates the liver cells to produce prothrombin which is one of the essential clotting elements

Another type of bleeding found in humans whose blood fails to coagulate is frequently associated with a decreased number of blood platelets and is characterized by the increased permeability of the capillaries so that blood may escape into the tissue spaces Removal of the spleen often benefits this condition, which is called *purpura* The number of platelets increases after its removal

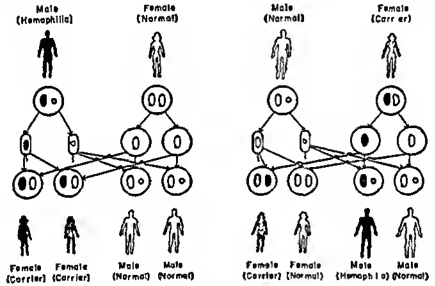


FIGURE 202

Illustrating the inheritance of hemophilia

Perhaps the best known of the bleeding or hemorrhagic conditions because of the publicity that has been given it, is *hemophilia* This is an inborn disease in which coagulation of the blood is so slow that sometimes a mere pinprick may produce such a severe hemorrhage that the afflicted person will die It is an inherited defect that affects only males although females may be carriers of the genes for the disease In other words it is a sex linked inheritance, the gene for hemophilia is evidently contained within the X-chromosome The disease has appeared frequently in some of the royal families of Europe because of intermarriage

As indicated in Figure 202 only men are bleeders Females who carry

the gene for the disease show no evidence, whatever, that the clotting time of their blood is anything but normal. Thus, in a cross between a "bleeder" male and a normal female, all the daughters would be carriers, the sons normal. If a female carrier is crossed with a normal male, approximately half the daughters will be carriers and half the sons, bleeders; the remainder of the offspring will be normal. Although it is possible for a female carrier and a "bleeder" male to have a hemophilic daughter, this occurs so rarely that it is generally considered that hemophilia does not occur in females.

The gene for hemophilia is a recessive and in a carrier female the one chromosome carries the gene for this condition whereas the other carries a normal gene, which is dominant and prevents the former from having its effect. In the male, however, there is only one X-chromosome—the Y-chromosome does not carry either a normal gene or a gene for hemophilia. Therefore, if the X-chromosome contains this gene, there is no other to show dominance and the hemophilic gene has its full effect.

The actual cause of the failure of the blood to clot in persons with hemophilia is not fully understood. Their blood platelets are known to take an extremely long time to disintegrate; and they show considerable stability. All of the other substances necessary for coagulation appear to be normal. Possibly the cause may be in the plasma of the hemophilic, since it has been found that the platelets of such blood will disintegrate normally if they are placed in normal plasma.

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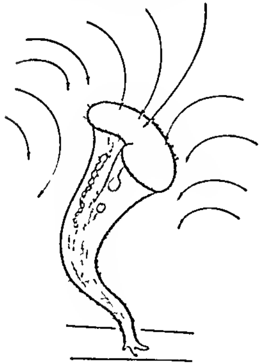
24

Development of a Fluid Circulation in Animals

CIRCULATORY SYSTEM OF INVERTEBRATES

THE LOWEST FORMS of invertebrate animals do not need a circulatory system. However, although nothing is found in the Protozoa resembling such a system, many of them have a means of securing and carrying food materials as well as oxygen and of getting rid of wastes by a circulation of the water surrounding them or by streaming movements within them. For example, the *Amoeba* accomplishes its type of locomotion partly by inward streaming of its protoplasm which also mixes up dissolved materials including gases, and conveys them to all parts of the cell. In *Paramecium*, food vacuoles are carried through the protoplasm by means of a streaming movement called cyclosis. As the organisms move along the food materials in them are digested and pass out of the vacuole into the protoplasm. Some



forms of ciliates such as *Stentor*, which attach themselves to various objects in ponds produce a circulation of the water surrounding them by co ordinated beats of their cilia The currents thus produced in the water carry food materials and fresh supplies of oxygenated water to the mouth opening of the stentor

The *sponges* (*Porifera*) have great numbers of small pores opening into a central cavity Water enters these pores and is forced out of the large *osculum* by the beating of the flagellated (choanocyte) cells that line the walls of the cavity (Figure 33 page 51) An actual pressure is developed in the central cavity of some sponges and although not very high, it may reach 4 mm H_2O pressure The amount of water that passes through some sponges in the course of twenty four hours may be very great In some species 70 to 80 liters per day have been reported from a single osculum This is probably the most primitive type of circulation in any way compara ble to the circulation of higher animals The same purpose is accom plished in both types food materials and oxygen are brought into contact with the cells of the body and waste products are carried away

The *Coelenterata* have gastrovascular cavities into which fluid contain ing food materials passes In *Hydra* (Figure 34 page 52) this is a simple saclike structure in which the water is circulated by the beating of the flagella of the cells lining the cavity In higher coelenterates such as medusae there are many saccular extensions which carry materials to more distant cells The streaming in these canals is well marked

The *Platyhelminthes* (*Planaria* for example) have not advanced much further than some of the higher coelenterates in relation to a circulatory system The materials are carried into the cavity of the worms and wastes are thrown out by way of the same opening In *Annelida* however, the

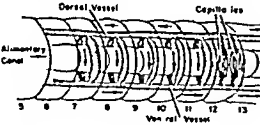


FIGURE 204

The hearts of an earthworm The body segments are numbered

transport system has become a truly circulatory one It is of the closed type consisting of two main vessels the *dorsal* through which the blood flows to the anterior part of the body and the *ventral* through which it flows to the posterior part This flow is produced by five paired pulsating vessels which connect the dorsal and ventral vessels in the seventh to

eleventh segments inclusive (Figure 204), these pairs are called "hearts" and they pulsate in such a way as to send the blood from the dorsal to the ventral vessel. The blood passes through capillaries in each segment as indicated in the figure, those in the skin area taking up oxygen which diffuses through the skin. The earthworm has no special respiratory area other than the skin itself.

The vascular system of the *Insecta* is an open circulation and is rather incomplete. It consists of a tubular heart which lies in the abdominal region and is made up of a series of saclike chambers which may vary in number. Each of these chambers is supplied with a pair of openings, one

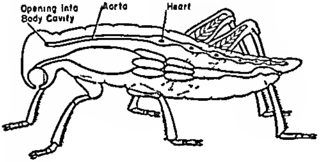


FIGURE 205

The circulatory system of the grasshopper

on each side, by means of which the lymph enters the heart. Generally the last chamber is closed at its posterior end so that the lymph can escape only by way of the anterior vessel called the *aorta* which opens in the head region. The insect circulatory system ensures a constant flow of lymph through the body and in this manner functions chiefly as a means of transporting food and excretory materials.

CIRCULATORY SYSTEMS OF VERTEBRATES

In the primitive chordate, *Amphioxus*, it is difficult to say whether or not a true heart is represented in the circulatory system. It depends upon the definition of a heart. Certainly pumping action is produced by the contraction of the ventral vessel. This, at least, is analogous to the hearts of higher vertebrates. *Amphioxus* has a *portal* circulation which is not found in animals of lower phyla. This part of the circulation consists of vessels that lead from the intestines to the liver. The blood in these vessels first passes through the capillaries of the intestine which unite to form the portal vein. The portal vein, in turn, breaks up into capillaries in the liver. The liver capillaries unite to form the hepatic vein which carries the blood back to the ventral aorta.

In fishes, the heart has lost its true tubular structure. Although simpler,

morphologically, the function of the fish heart is the same as that for the hearts of all other classes of vertebrates. It is composed of two main chambers, one *auricle* or *atrium* and one *ventricle*. The veins of the fish heart empty into a saclike structure, or chamber, the *sinus venosus*, which leads directly into the auricle, another lesser chamber, the *bulbus arteriosus* or *conus arteriosus*, is found between the ventricle and aorta (Figure 206). All four chambers have the power to contract and do so in proper sequence so that the blood flows only in one direction. The valves between auricle and ventricle and between ventricle and *conus arteriosus* prevent a backflow of the blood.

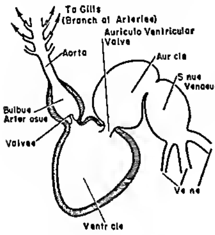


FIGURE 206

The fish heart: it consists of two main chambers, an auricle and ventricle.

The ventral aorta of the fish gives off afferent branches that lead to the gills and break up into capillaries, which unite again to form the efferent vessels that lead to the dorsal aorta. Thus as the blood passes through the gills, it becomes oxygenated and loses carbon dioxide.

The *amphibian heart* consists of a *sinus venosus*, two auricles, one ventricle and a *bulbus arteriosus* (Figure 207).

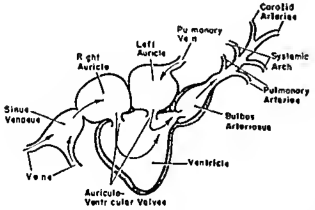


FIGURE 207

The frog heart: a three chambered heart consisting of two auricles and one ventricle.

Except for that found in the pulmonary vein leading from the lungs the blood of amphibians is never saturated with oxygen. There is an arrangement, however, by means of which the partially oxygenated and fully oxygenated blood tend to remain separate in the ventricle also, when the

ventricle contracts, the first blood to leave is the venous blood which had just entered the ventricle from the right auricle Since there is less resistance in the pulmonary arteries than in the systemic, the venous blood which is forced out of the heart first, enters these vessels and goes, by way of the pulmocutaneous artery to the lungs and skin where it is oxygenated

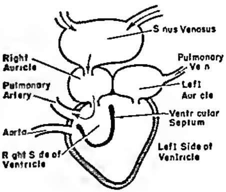


FIGURE 208

The reptilian heart a three chambered heart which approaches a four chambered heart in the higher reptiles

In the *reptilian heart* are found approximately the same structures as in the amphibian except that a muscular septum has formed which tends to separate venous and arterial blood and the *bulbous arteriosus* is rudimentary This septum completely separates the two ventricles in the crocodile, but in the lower reptiles such as snakes lizards, and turtles it is incomplete and some of the blood may mix The reptilian heart shows the presence of a coronary system which is not true of the hearts of amphibians and those of most fishes

The hearts and circulation of birds and mammals are quite similar so that any discussion concerning the one should apply also to the other

EARLY DISCOVERIES PERTAINING TO HUMAN CIRCULATION

Every high school student and most grade school students today have a general idea as to how the blood circulates in the body, but before the invention of the microscope and the discovery of capillaries physicians and scientists did not understand the passage of the blood from arteries to veins by way of capillaries The capillaries have a diameter of eight to ten microns, which is only slightly greater than the diameter of the red blood cells

Hippocrates a Greek physician who lived about 400 B C, recognized the fact that the heart is muscular and that its beating results in the pulsations of the blood vessels Aristotle (about 350 B C), famed for his many works in natural history, understood the heart to be the center of the blood vessel system However, he also suggested that it was the center of intelligence, a view that is still carried over to our present time in the common expression to learn a thing by heart"

A Roman physician, Galen (about 180 A D), was the first to prove that an artery contained blood and not air When a body is opened after death

from arteries to veins through the small tubular structures now called capillaries This was the final proof of what Harvey had earlier postulated

ADDITIONAL READING

Clendening, L , *Source Book of Medical History* (New York Hoeber, 1942), pp 42–45, 152–169 Galen on the pulse, Harvey on circulation

Mettler, C C , *History of Medicine* (Blakiston, 1947), pp 431–442, 515–524 Early studies on circulation, work of Harvey and Malpighi

most of the blood has settled in the smaller vessels (which are dilated because of loss of tonus), leaving the arteries empty, thus arose the early conception that they normally contained air Galen disproved this by tying an artery in two places in a living animal and then cutting between the ligatures In this way he found that blood and not air was present in it

Galen thought that the blood flowed back and forth in the vessels in the same manner as the ebb and flow of tides, and, because he knew nothing of the existence of capillaries, he believed that there were openings in the septa separating the two ventricles as well as in those separating the two auricles The blood supposedly passed into the left ventricle and auricle by way of these openings and there mixed with air coming from the lungs Of course, in the adult, this is not true but in the very early embryo there is a direct opening between the two ventricles which finally closes in a later embryonic stage There is, however, an opening between the two auricles of the heart which remains open for a much longer time In fact, it does not close until birth, when the first breath of air is taken This is discussed later under fetal circulation (page 336)

The work of Galen, including his ideas of the heart and circulation, was used as a basis for medical education until the time of Harvey (1628)

Leonardo da Vinci, who lived between 1452 and 1519 A.D., was evidently not too far from the discovery of the circulation as can be seen from some of his drawings and sketches Evidently he knew the function of the heart, at least he realized that "the heart shortens itself during its expulsion of the blood"

from arteries to veins through the small tubular structures now called capillaries This was the final proof of what Harvey had earlier postulated

ADDITIONAL READING

Clendening, L , *Source Book of Medical History* (New York Hoeber, 1942), pp 42–45, 152–169 Galen on the pulse, Harvey on circulation
Mettler, C C , *History of Medicine* (Blakiston 1947), pp 431–442, 515–524 Early studies on circulation, work of Harvey and Malpighi

25

The Heart

THE HUMAN HEART

THE HEART is the pump by means of which the blood is kept moving in the blood vessels, so arranged in the body as to make a complete cycle possible. In other words, the circulation is a closed system, there being no openings into the tissues. A steady flow of blood continues through the capillaries where exchange of materials can be made with the tissue fluid by means of diffusion through the capillary wall. The heart begins beating rhythmically early in embryonic life and continues until death. Thus, during an average lifetime of sixty five to seventy years, the amount of blood passing through the heart is enormous. If we consider only the heart rate while the body is at rest (70 to 90 beats per minute), it will contract about 3 billion times and move between 150 million to 200 million liters of blood.

The heart is made up of cardiac muscle tissue called the *myocardium*. Internally, it is lined with endothelial cells forming a membrane known as the *endocardium*. This layer of cells is continuous with the inner lining of the arteries and veins and the wall of the capillaries. The whole structure is surrounded by a membranous sac, the *pericardium*, which is actually made up of two layers with a cavity between, containing the pericardial fluid. The cavity is not very large, containing only a few drops of fluid for lubricating the walls of the sac.

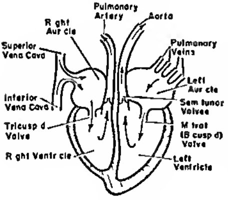


FIGURE 209

Diagram of a mammalian heart

The Chambers of the Heart

The human heart, as well as that of all other mammals and birds, has four chambers. These are illustrated in Figure 209. The two upper chambers, into which the veins empty, are the *auricles* or *atria*. The large veins, the *superior vena cava*, which returns the blood from the head, shoulders,

and arms, and the *inferior vena cava* which returns it from the trunk and lower limbs, empty into the right auricle The four *pulmonary veins* empty into the left auricle

Contractions of the two auricles, which act simultaneously, aid in pumping the blood into the *ventricles* There is no need of any great force to accomplish this and the ventricles, when they relax, draw blood down from the auricles in a sucking action Evidently for this reason, the walls of the auricles are rather thin and contract somewhat feebly

The ventricles have much thicker walls than the auricles, because of the greater work they must do in forcing the blood to all parts of the body

THE PULMONARY AND SYSTEMIC CIRCUITS

There are two channels by way of which the blood leaves the ventricles, the *pulmonary artery* and the *aorta* The first is referred to as the *pulmonary circuit*, the latter the *systemic circuit* The pulmonary artery carries blood from the right ventricle to the lungs, whereas the aorta carries the blood to smaller channels that reach all other parts of the body

Subdivisions in the systemic circuit include the *coronary circuit* which feeds the heart itself and the *portal circuit* which carries blood to the alimentary tract, the spleen, the pancreas and the liver Within these organs the arteries of the portal system divide into capillaries that unite to form the portal vein leading to the liver, and there again breaking up into capillaries The hepatic vein then carries the blood to the inferior *vena cava*

A schema of these circuits and the chief parts of the body reached by them are presented in Figure 210 The systemic circuit, as compared with the pulmonary, is rather extensive, the force needed to carry the blood through it is very great The blood pressure in the right ventricle when contracting reaches about 30 mm mercury, whereas that in the left ventricle may reach 150 mm or more For this reason, the musculature of the right ventricle is not so great as that of the left since the right need only pump the

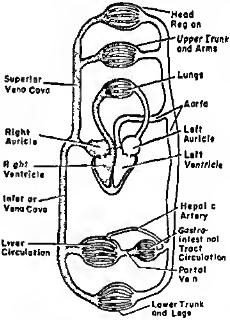


FIGURE 210

Schema of human circulation

blood through the lungs which are close at hand and on the same level as the heart

The blood is forced out of each auricle simultaneously by contraction,

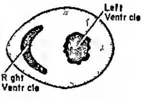


FIGURE 211

Section through ventricles of dog heart to illustrate shape of ventricles and their comparative thicknesses

this is true also for the ventricles The contraction phase of the heart is referred to as *systole*, the relaxation and rest periods as *diastole*

FETAL CIRCULATION

The circulation of a developing mammal alters several times during pregnancy or gestation in order to accommodate the changes due to growth of the embryo and fetus There is a special division of the circulation which is necessary in the embryo and fetus because the lungs and the digestive tract cannot function until after birth This division is called the *umbilical* circuit which consists of one *umbilical vein* carrying blood from the placenta to the fetus and two *umbilical arteries* carrying blood back to the placenta The fetus is entirely dependent upon the mother for its oxygen and food materials although there is no direct connection between the blood stream of mother and fetus It is generally known that this transfer of substances is accomplished by diffusion of these materials from the uterine capillaries of the mother into the blood sinuses of the placenta

The umbilical vein divides into two branches soon after its entrance into the body of the fetus One branch the *ductus venosus*, enters the portal vein just before it reaches the liver, and the other branch unites with the inferior *vena cava* From this point of union until it reaches the right auricle the *vena cava* contains a mixture of arterial and venous blood when it arrives at the entrance to the auricle it is mixed with additional venous blood from the superior *vena cava* Much of the blood that enters the right auricle passes directly through an opening the *foramen ovale*, to the left auricle Some of the blood goes to the right ventricle and is pumped out through the pulmonary artery toward the lungs However, the lungs are not functional at this time and need blood only for their general metabolism and growth For this reason, most of the blood leaving the right ventricle by way of the pulmonary artery passes into the aorta by way of a special fetal vessel, the *ductus arteriosus* This structure is only tem

porary and begins to contract when respiration is initiated at the time of parturition (childbirth). The lumen of the vessel is slowly obliterated so that only a ligament remains when the change is completed. The *foramen ovale*, the opening which allows blood to enter the left auricle from the right, has become very small by the time of birth. A tissue membrane or flap grows downward over the opening and normally causes complete closure toward the end of the first year of life. Sometimes, however, it does not close properly.

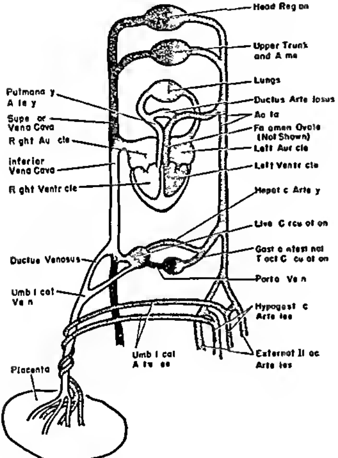


FIGURE 212

Diagram of the fetal circulation

A child suffering from such a defect never has fully oxygenated blood flowing through his systemic circuit. In fact, fully oxygenated blood would be found only in the pulmonary veins and this blood on reaching the left auricle, is mixed with the venous blood which has passed through the opening from the right auricle. For this reason the skin of these children may be bluish; thus they are sometimes referred to as "blue babies." If the condition continues, the child usually dies at an early age. Today

however the condition is sometimes remedied by a rather difficult operation

It is clear that the blood of the fetus must pass through more numerous and diverse pathways than that of the adult However the vessels in these strictly fetal circuits *ductus arteriosus foramen ovale ductus venosus* the hypogastric arteries and the umbilical artery and veins vanish soon after birth although sometimes several days are required for complete disappearance

THE VALVES OF THE HEART

The heart action is that of a mechanical force pump the blood within it must be prevented from flowing in more than one direction This is accomplished by valves which are located in appropriate positions within the heart The valves are shown diagrammatically, in Figure 213

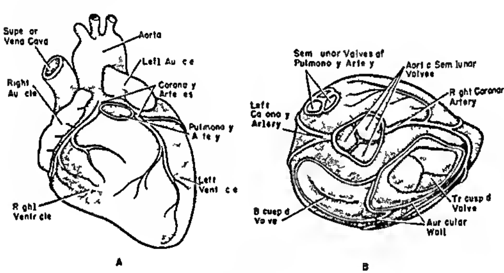


FIGURE 213

A the external structure of the heart B view of heart from above with auricles and arteries cut away

Starting in the auricles the blood flows through openings into the ventricles The chambers of the heart open and close in harmony with one another so that when the auricles are contracting and forcing the blood into the ventricles the latter are relaxed and at rest contracting only after the auricles begin to relax When the ventricles contract the true nature of the orifices between them and the auricles is discovered Actually the openings are valves which open only on relaxation of the ventricles and close when they contract These valves are called the auriculo-ventricular valves

That on the right side of the heart is sometimes called the *tricuspid* because it has three flaps, that on the left, the *mitral* or *bicuspid*

From the edges of these valves are found cordlike structures (the *chordae tendineae*) that lead down to the *papillary muscles* originating in the ventricular walls These structures prevent the valves from being forced upward when the ventricle contracts The force of ventricular systole would be great enough to do this if the papillary muscles did not contract at the same time as the rest of the ventricle and in this way pull down on the valves by means of the tendonlike cords

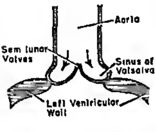


FIGURE 214

Structure of aorta and heart tissue at point of juncture

The *semilunar valves* are located between the right ventricle and pulmonary artery and between the left ventricle and aorta In each case, they consist of three flaps at the point where heart and artery join When the artery is opened, the flaps observed resemble half moons They form pockets, and when the blood is forced through the vessels the semilunar valves are flattened by the pressure They are prevented from sticking to the walls of the great arteries by a peculiar distention at the point of union with the heart, called the *sinus of Valsalva* A certain amount of blood always remains in these pockets

The semilunar valves open when the force of the ventricular contraction is strong enough to produce a pressure greater than that already present in the pulmonary artery and aorta They close at ventricular diastole

THE CARDIAC CYCLE

As pointed out previously, the heart acts as a pump in a manner similar to the rubber bulb of an atomizer, valves are arranged in both heart and atomizer bulb in such a way as to prevent a backflow

Each contraction or systole of the heart is followed by diastole which consists of relaxation and rest, all of which constitute the *cardiac cycle* The cardiac cycles of various animals differ, and, as a general rule, it is found that the heart rate varies indirectly with increase in size, especially for warm blooded animals This is well illustrated in Tables 12 and 13 Table 12 shows the number of beats per second for some mammals at rest.

Table 13 shows the basal and maximal rates for birds of different species

TABLE 12

Rate of Heartbeat in Various Mammals

Animal	*Heartbeats Per Minute*
Elephant	25
Horse	50
Sheep	70
Man	70–90
Dog	100
Rabbit	150
Rat	250–300

TABLE 13

Basal and Maximal Rates of Heartbeat for Birds of Different Species

Species	*Approximate Weight in Grams*	*Heartbeats Per Minute* Basal Rate	Maximal Rate
Mourning dove	130	135	570
Cardinal	40	375	800
Canary	16	514	1000+
Chipping sparrow	12	440	1060
Ruby-throated hummingbird	4	615	?

The heart rate seems to vary indirectly with increase in size This is expected for it is obvious that the smaller an animal the larger, proportionately is the surface exposed to the external environment Thus there is relatively much more heat lost in a very small animal which necessitates a higher metabolic rate and, hence, a more rapid blood flow

In humans the heartbeat varies in the same manner as in other warm blooded animals That is, the younger (and smaller) the individual, the more rapid is the rate These different rates are shown in Table 14

Frequently, it is claimed that, because there is occasionally a slight difference in the heart rate of the female and the male fetus, it is possible to foretell the sex of a child. The heart of the female fetus is said to beat at the rate of 140 to 145 times per minute and that of the male between 130 to 135 times. However, there are so many variables, such as muscular movement and position, that this method is hardly dependable.

The heartbeat starts in the right auricle near the entrance of the veins. The two auricles contract practically at the same time. Their contractions force blood into the ventricles which are relaxed and at rest and will extend readily to even slight pressure. There is just a small fraction of a second between the end of auricular systole and the beginning of ventricular systole; this is the time during which the impulse passes over the ventricles.

At the beginning of ventricular systole the auriculo-ventricular valves snap shut producing the *first heart sound*. The blood within the chamber does not move for a small fraction of a second after the beginning of ventricular contraction. This is called the *first isometric period*. The ventricles

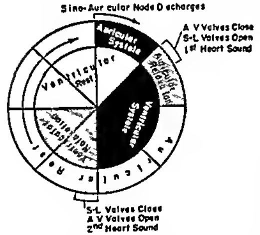


FIGURE 215

The cardiac cycle. The diagram represents a cycle of 0.8 sec. duration and is divided into 8 sections of 0.1 sec. each. The outer circle represents the auricular cycle, the inner circle the ventricular. The dark areas represent systole, the lined areas relaxation. Diastole is relaxation and rest.

must contract sufficiently to overcome the pressures still present in the pulmonary artery and aorta, respectively, before the blood can flow into them. The residual pressure of the aorta (that is, the least pressure) is about 70 mm. mercury. This is considerably greater than that in the pulmonary artery. After the blood is ejected (about 60 cc. per beat at rest) at the height of ventricular contraction, the ventricles begin to relax and as they do so, the blood in the arteries tends to flow back but some of it catches in the flaps of the semilunar valves and forces them shut with a snap resulting in the *second heart sound*. Again, there is a small fraction of a second when no blood flows into or out of the ventricles; this is called the *second isometric period*. The ventricles finally relax sufficiently to allow the auriculo-ventricular valves to open and the blood which had been

collecting in the auricles, then flows into the ventricles This process is repeated in humans at the rate of about seventy times per minute when the body is at rest

During this time almost all the 5000 to 6000 cc of blood in the body passes through the heart If the body is active the blood passes through it much more rapidly The time relations of the events just described are represented in Figure 215 The average time of a complete cycle is taken as 0 8 sec The diagram is divided into eight segments each representing 0 1 sec The outer circle represents the events occurring in the auricles, and the inner circle, those occurring in the ventricles It will be noted that during much of the time required for the cardiac cycle the musculature is at rest This enables the heart to function steadily and rhythmically with little danger of fatigue

VALVULAR LEAKAGES

When any one of the valves fails to close perfectly, a leakage occurs Valvular leakages are among the common heart ailments often being present in childhood but disappearing as the children grow older

The seriousness of the effects on the body depends upon the valves affected and the degree of the defect If the semilunar valves leak a jet of blood is forced back into the ventricles This of course, means that the heart does not pump sufficient blood at each systole It compensates for this by enlarging the cardiac muscle increases in size, a condition known as *hypertrophy* In this way the heart becomes powerful enough to force enough blood out at each beat so that the tissues will obtain an adequate amount although some blood seeps back into the ventricles

If the auriculo-ventricular valves leak the condition is much more serious than in the case of semilunar valve leakages The powerful ventricular beat will force blood backward through the A V valves and produce such a back pressure in some of the veins that the venules and capillaries leading to them may be damaged Obviously if the bicuspid valve leaks the capillaries of the lungs are damaged whereas, if the tricuspid leaks, those of vital organs such as the kidney and liver are injured

REGULATION OF THE HEARTBEAT

In most animals the heart continues to beat for varying lengths of time, even when it is removed from the body The heart of a vertebrate frog or mammal can be excised and if environmental conditions are favorable, go on beating rhythmically for hours Strips of heart can be cut away and still continue to beat In tissue culture, cardiac muscle cells contract

rhythmically although no nervous tissue is present. Thus, it appears that conditions initiating systole arise within the cardiac tissue itself. Such contractions are said to be *myogenic*. In these cases, then, nerves which lead to the heart are not essential for the beat itself, but rather for the regulation of the rate of contraction. As mentioned in the discussion of the autonomic nervous system (page 177), the heart rate is regulated by means of autonomic nerves. Parasympathetic fibers (vagi) are inhibitory, their normal secretion, acetylcholine, is inhibitory to the heart, even if the nerves have been severed. Sympathetic fibers from the thoracic region are stimulatory causing the heart to beat faster, adrenalin has the same effect.

On the other hand, if the heart of a crustacean is removed from the body, or only certain nerves leading to the heart are cut, the heart immediately stops beating. In this case, then, the nerves furnish the stimulus for contraction and the heart is said to be *neurogenic*. It is interesting to note that in this type of heart, acetylcholine may have a stimulating effect.

The vertebrate heart cannot be tetanized (page 65) because of its long refractory period, therefore, if impulses come to it too rapidly some of them are ineffective. The absolute refractory period (page 65) of the heart lasts as long as the contraction and is followed by a relative refractory or subnormal period.

THE FROG HEART

In the frog heart, the *sinus venosus* appears to be the "pacemaker" or the place from which the beat originates to spread out first over the auricles and then the ventricles. If the *sinus venosus* is cut away, it continues beating at its normal rate but the rest of the heart stops for a time and later starts again, but at a much slower rate than normal, with the auricles taking over the role of pacemaker. If a ligature is applied to the frog heart between the auricles and the ventricle, the former continue beating while the latter stops and may or may not start beating again. If it does, however, the rate is extremely slow.

It is obvious that a gradient of excitability exists over the heart, with the *sinus venosus* as a pacemaker, for the beat of auricles and ventricles follow in unison with that of the *sinus*.

THE MAMMALIAN HEART

In the mammalian heart there is a slight difference in structure from that in the frog heart. There is no saclike *sinus venosus*; this organ is present, however, as a rudimentary nodule on the right auricle at the entrance to the

veins It is called the *sino-auricular* (S A) *node* and is the *pacemaker* of the mammalian heart The node is made up of modified cardiac tissue consisting of cells that have lost most of their striations

The conduction wave (impulse) as well as the beat of the heart begins at the S A node, although how it is aroused to activity is not known The heart is most sensitive to temperature changes at this point Increase in temperature will increase the frequency of its discharge whereas conversely the frequency will be lessened with a lowering of the temperatures Impulses over the vagus or sympathetic nerves of the heart seem to be most effective at the S A node, the electrical wave, associated with conduction over the heart and its contraction, first making its appearance here

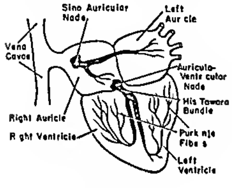


FIGURE 216

The conduction system of the heart

The rate of the conduction wave over the auricles is about one meter per second The impulse spreads over the entire auricular mass down to the *auriculo-ventricular node* From the A V node it spreads over the A V bundle (His Tawara bundle) at the rate of about five meters per second In the septum between the ventricles the A V bundle divides into the right and left branches which form within the muscular walls a meshwork of fibers known as *Purkinje* fibers The conduction wave, passing over these fibers, causes the contiguous cardiac muscle cells to contract

Three standard positions of the lead off electrodes are used for obtaining electrocardiograph records (I) one lead fastened to the right hand, the other to the left, (II) one lead to right hand, the other to left leg, (III) one lead to left hand, the other to left leg (Figure 217)

The electrical response differs in its intensity at different points along its course over the heart In Figure 218 is shown a copy of a record made with an electrocardiograph and the various elevations are lettered These letters are merely symbols and are used only for convenience The *P* wave records auricular excitation, it is the expression of the impulse flow over the auricles The auricles begin to contract before the impulse represented by the *P* wave ceases The *QRS* wave records ventricular excitation and the *T* wave is the return of the heart to normal rest The *PR* interval is the time when the impulse flows over to the A V bundle, the ventricles begin to contract at about the time the *QRS* wave reaches its greatest intensity The *T* wave is quite variable in shape and is sometimes inverted, often being used for detecting certain heart conditions that affect its extent and position

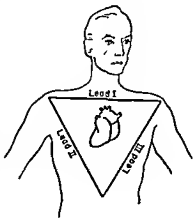
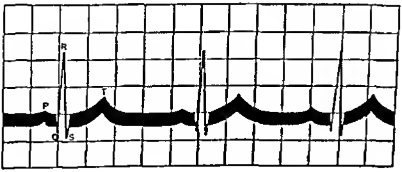


FIGURE 217

Diagram illustrating the different leads used for obtaining electrocardiograms in humans



HEART BLOCK

Many abnormal heart conditions may be diagnosed by means of the electrocardiograph Many of the failures of the heart in old age can be detected as well as the abnormalities resulting when syphilitic invasion and other infections produce nodules upon conductile structures of the heart If a nodule should form on the A V node it would gradually press on the conductile fibers and result in *partial heart block* in which there is a delayed conduction In a partial heart block (that is, 2 1 block) for every two auricular impulses, one passes over to the ventricles In terms of the electro cardiogram for every two P waves there is one QRS wave In *complete heart block* the auricles and ventricles do not beat in a properly coordinated fashion each having its own rhythm

OUTPUT OF THE HEART

About 60 to 70 cc of blood is forced out of the heart at each ventricular systole resulting in the movement of 4 to 5 liters per minute This is the total for the heart of an average man during rest There are many condi tions under which the heart increases its output During *exercise* the volume expelled from each ventricle per beat may double (120 to 140 cc blood), at the same time the heart rate may increase to 140 to 180 beats per minute Therefore, the total volume passing through the heart per minute may increase to nearly 35 liters in strenuous exercise Other condi tions under which there is an increased output are (1) *emotional excite ment*, (2) *high temperatures*, (3) *pregnancy*, (4) *digestion*, (5) *hyper thyroidism*, and (6) *anemia* The output is decreased in (1) *hypothyroid ism* (2) *malnutrition*, (3) *rest*, and (4) *various heart diseases*

THE LAW OF THE HEART

The heart is organized extremely well with respect to its activity When the tissues of a healthy individual need more blood, the heart manages to send more blood to them As already pointed out, there is an increase in the volume of blood forced out at each ventricular beat This de pends upon a fundamental property of cardiac muscle enabling it to produce a much more powerful contraction when stretched This phe nomenon, also a property of all striated muscle, is known as The Law of the Heart' The circumstances under which the law works in the heart include an increase in the amount of blood flowing from the veins into the auricles Thus a greater amount is forced into the ventricles which are at rest and hence quite flabby and yielding The large quantity of blood stretches the ventricles more than usual making their contractions more

powerful The force of the contractions corresponds to the amount of stretching, within reasonable limits

THE BAINBRIDGE REFLEX

The Bainbridge reflex works hand in hand with the Law of the Heart This reflex involves an increase in the rate of heartbeat and is initiated by the stimulation of stretch (pressure) receptors in the walls of the *venae cavae* as they enter the heart An increase in venous blood pressure (such as that caused by an increased venous return, due to muscular massage of the veins during exercise) stimulates these receptors to send impulses to the centers in the medulla The impulses then pass over to association neurons connecting with the sympathetic fibers (accelerator nerve) that lead to the heart, and thus cause an increase in beat

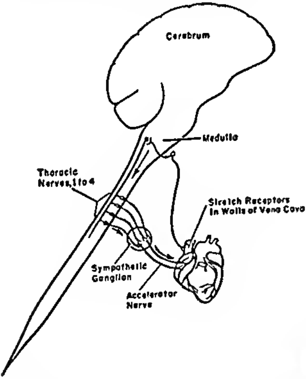


FIGURE 219

Diagram illustrating the impulse pathways of the Bainbridge reflex

These properties of the cardiovascular tissues enable the heart to increase its output from about 4 or 5 liters per minute to as much as 35 liters per minute

ADDITIONAL READING

Gray, H *Anatomy of the Human Body*, 25th ed (Philadelphia Lea and Febiger 1948), pp 527–548 The heart in the fetus and adult
Prosser C L, *Comparative Animal Physiology* (Saunders 1950) ch 15 Vertebrate and invertebrate hearts

Flow and Pressure of Blood in the Vessels

THE FLOW OF BLOOD

THE BLOOD flowing at the rate of 30 to 50 cm per second in the large arteries pulsates as the result of the intermittent flow from the ventricle The frequency of the pulsations coincides with the ventricular contractions the pulsations disappearing when the blood reaches the arterioles and capillaries the venous flow also is steady One can note this difference in the flow of blood resulting when an artery is cut as compared with that resulting when a vein is cut the blood escapes from the artery in spurts whereas it flows from the vein in a steady stream

Several factors are associated with the steady flow of blood in arterioles and capillaries and consequently the veins First the friction of the blood against the walls of the vessel becomes greater as the vessel diameter decreases This phenomenon referred to as peripheral resistance is effective partly in obliterating the pulsations Second the arterial walls are very elastic tending to expand with the increased pressure of systole This expansion is a means for preventing too high blood pressure normally, and is also a factor in producing a steady flow Third the area of the capillaries far exceeds that of the arteries thus the speed of the blood flow, as well as its pulsatile movement, is diminished In other words such an arrangement would be similar to the flow of a swift stream of water emptying into a broad lake, since there also the speed and unsteady flow tend to diminish because of the great increase in area

SIZE OF THE BLOOD VESSELS

The aorta is about 30 mm in diameter and as it divides into an increasingly greater number of smaller arteries whose diameters decrease progressively, the total cross sectional area increases In other words, the aorta divides into smaller arteries which in turn divide into still smaller ones and so on, the smallest subdivisions being known as the arterioles These vessels usually divide into twenty to fifty capillaries which reunite forming

venules which, in turn, form small veins, these give rise to larger ones, and so on, until at last the largest veins unite to become the *venae cavae*

In skeletal muscle there are about 30,000,000 capillaries per cubic inch The number of capillaries, always large, varies, some tissues having fewer than the skeletal muscle, others more The average diameter of the capillary is 8 to 10 microns, its average length, 0 5 mm It has been calculated that if all the capillaries were placed end to end, their total length would reach 60,000 to 65,000 miles The total surface area of the capillaries referred to as the capillary lake is enormous, being about 500 to 600 times as great as that of the aorta It has been calculated that the total *surface* area of the capillaries may be greater than 60,000 square meters (10 acres) The rate of flow in the aorta, about 250 to 500 mm per second, has decreased to 0 5 to 1 mm per second by the time it reaches the capillaries

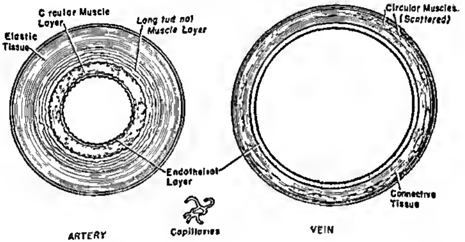


FIGURE 220

Comparison of structure of an artery with that of vein Outline of capillaries showing comparative size

THE ARTERIAL WALL

Endothelial cells, forming a structure known as "the endothelium," compose the inner walls of the arteries This endothelium is continuous throughout the vascular system and can be traced from the capillaries to the arteries, the heart and the veins From the capillaries back to the heart, the artery walls become increasingly thicker In the smaller arteries and arterioles, a thin sheath of connective tissue immediately surrounds the endothelial layer, in turn surrounded by smooth muscle cells (forming a longitudinal layer and a circular layer) Immediately external to the smooth muscle layer is a layer of connective tissue

No smooth muscles occur in the largest of all arteries, the aorta. About fifty layers of elastic connective tissue, however, form concentric rings around the vessel, enabling it to expand but, at the same time, to retain considerable thickness and sufficient strength to withstand the force of each ejection of blood from the ventricle.

THE CAPILLARY WALL

The capillary wall is composed of endothelial cells, stretched considerably to form a very thin membrane, and held together by an "intercellular cement." Some connective tissue cells surround the capillaries and give support to their walls. Scattered about on the exterior surface are numerous *Rouget* cells having pseudopodialike processes that surround the capillary. The function of these cells is still obscure. At one time they were thought

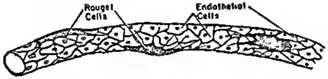


FIGURE 221

Capillary structure and Rouget cells.

to be contractile and thus to cause constriction of the capillaries, but this is doubtful, the endothelial cells themselves are contractile and carry out this function very well.

The capillary wall is about 1 micron thick and is permeable to water and many soluble crystalloids, such as glucose, amino acids, salts, urea, creatine and creatinine. It is not permeable to the red blood corpuscles, but some of the plasma proteins and hemoglobin, if set free in the plasma, will pass through. Occasionally, large objects, such as white cells and parasitic worms, pass from the blood in the capillary into the surrounding tissue spaces without injury to the capillary wall. Probably they accomplish this by forcing their way through at the junctures of endothelial cells.

CAPILLARY FUNCTION

The exchange of materials between the blood and tissue spaces takes place only through the capillary wall; this is true also for the exchange of food materials in the intestine as well as for the exchange of oxygen and carbon dioxide in the lungs.

Conditions within the tissues regulate to some extent the blood flow in the capillaries. For example, an adequate supply of oxygen in the tissues is a stimulus initiating constriction of the capillaries. Adrenalin and pituitrin also cause constriction. On the other hand, an increase in acidity,

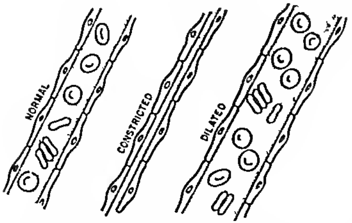


FIGURE 222

The normal constricted and dilated states of blood capillaries

due to *concentration of waste products in the tissues, results in dilation of* the capillaries. This increase in capillary diameter is noticed also in the victims of wound or surgical shock, or on application of *histamine*, a substance liberated by injured tissues.

THE WALLS OF THE VEINS

The walls of the veins are much thinner than the walls of their corresponding arteries (Figure 220), in spite of their having, as do the small

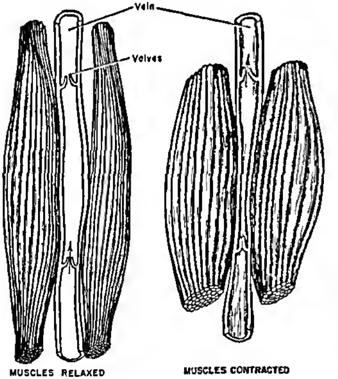


FIGURE 223

Illustrating the action of the valves in the veins and the muscular facilitation of blood flow in the veins of the legs. The blood is forced from one level to the next by means of the squeezing action of the muscles.

arteries and arterioles, a smooth muscle layer surrounding the endothelium At most, the walls of the veins are no more than 0 5 mm in thickness The blood flowing through them, at a rate about half that flowing through the arteries, averages about 200 mm per second

The small veins have in their walls valves that open to allow blood to flow toward the heart, but, because of gravity or some other force, they close when the blood tends to flow away from the heart Because the valves are needed for the normal return of the blood to the heart, they are quite numerous in the veins of the limbs The contractions of the limb muscles (especially those of the legs) facilitate the forward movement of the blood by pressing against the blood contained in the veins Since valves prevent its backflow the blood can move in only one direction

No valves are present in the *venae cavae* or in the veins leading from the head and neck

ARTERIAL BLOOD PRESSURE

Arterial blood pressure is of extreme importance to the body Blood pressure may be defined as that pressure exerted by the blood upon the walls of the vessels and the heart comprising a closed circulatory system The arterial blood pressure must be great enough to ensure an adequate supply of blood to the tissues If it is not sufficiently great, the blood supply to the brain and other tissues is diminished, a condition which may lead to dizziness and fainting On the other hand, if the pressure becomes too great, especially in the vessels of the brain, it may cause the rupture of a vessel, resulting in a hemorrhage This condition, commonly called a 'stroke,' occurs occasionally in older people who have developed high blood pressure

MAINTENANCE OF BLOOD PRESSURE

Many factors are responsible for the maintenance of blood pressure, the chief of which are discussed below

1 *Systole of the left ventricle* Obviously, the greater the force of the *ventricular beat* and the greater the volume of blood ejected by the ventricles, the greater will be the pressure of the blood in the arteries, if less blood is expelled with each ventricular beat, the arterial pressure is lowered This is true, however, only if the other factors concerned with blood pressure do not change

2 *Peripheral resistance* This is caused by the friction of the blood against the walls of the vessels The smaller the lumen of the vessel, the greater will be the friction, hence, the slower will be the blood flow, since

the pressure increases with the resistance Thus vasoconstriction causes increase in pressure vasodilation decrease in pressure

3 *The volume of blood as compared to the capacity of the circulatory system* Normally there is sufficient blood to fill the vessels and actually to cause stretching Because the vessels are elastic they are capable of being stretched However there may be too great an increase in blood volume that is an increase to the point where the arteries cannot stretch further (the pressure may become great enough to rupture vessels in the brain or elsewhere) There may also be a decrease in volume reaching such a low level that shock may develop due to lowered pressure

Within any closed system the internal pressure will vary inversely with the volume of that system thus the *volume of the circulatory system* influences blood pressure If the smooth muscle in many of the vessels is made to contract to a greater degree causing the diameter of the vessels to become less then more pressure is placed upon the elastic walls of the vessels with the result that the blood pressure is increased Conversely if the vessels are dilated the internal pressure is diminished Certain nerves that control the degree of contraction of smooth muscle in blood vessels are therefore very important as controlling factors of blood pressure When one becomes angry certain nerves cause the heart to pump more blood and some of the blood vessels to constrict with the result that blood pressure increases and the blood flows more efficiently

4 *The elasticity of the arterial walls* If it were not for the *elasticity* of the arterial walls there would be a much greater range of pressure in the blood vessels As already pointed out the artery walls are well supplied with elastic connective tissue When blood is forced into the arteries at each beat of the ventricle they stretch and exert a force on the blood with the result that there is always considerable positive pressure within them

5 *The viscosity of the blood* The *viscosity* or thickness of blood is greater than that of water thus because friction is greater blood flows more slowly through a tube For this same reason a greater pressure is built up than would be developed if the viscosity were lower

METHODS OF ASCERTAINING BLOOD PRESSURE

The *direct method* of ascertaining blood pressure is not practical for man but may be used for other animals In this method the vessel is actually opened and by means of a cannula the blood is brought into direct contact with the recording instrument—a manometer

In the first known attempt to measure blood pressure the direct method was used Stephen Hales in 1733 cannulated the artery in the groin of a

horse, the cannula being then connected with a glass tube 9 ft in length and ⅙ in in diameter The blood rose in this tube to a height of about 8 ft This method was simplified later by using a U shaped manometer with mercury which has a specific gravity of 13 5 in the tube, thus, a much shorter tube can be used It would be impossible to measure human blood pressure as a standard procedure if we had to use the direct method

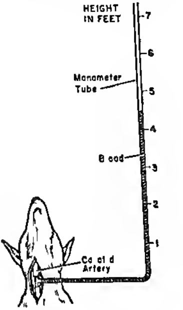


FIGURE 224

Direct method of ascertaining blood pressure Cannula with connecting tube in carotid artery of a dog Blood rises in tube to height of about four and one half feet

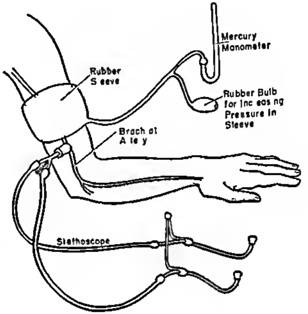


FIGURE 225

Diagram illustrating the use of the sphygmomanometer in measurement of human blood pressure

In the *indirect method* the blood vessels are left intact Today, we employ a form of an apparatus called the *sphygmomanometer*, by means of which the existing pressure within an artery, such as the brachial artery, is accurately balanced by a known pressure regulated in the artificial system surrounding the artery, in the case of the brachial artery the arm band of the apparatus is applied around the upper arm

In measuring blood pressure an arm band (or rubber sleeve) containing a rubber bag is wrapped tightly around the arm (Figure 225) The bag is connected with a rubber bulb and a mercury or an aneroid manometer The arrangement allows for inflation of the rubber bag by means of the bulb and, at the same time the pressure within it is recorded by the mercury

in the manometer (or by movement of a marker in the case of the anaeroid type). In one method, the observer feels the pulse of the subject or patient with one hand and inflates the rubber arm bag until the manometer registers a pressure believed to be higher than the subject's arterial pressure, that is, between 130 and 150 mm of mercury (Hg) pressure If this is done, the observer can no longer feel the pulse because the pressure in the bag is sufficient to close the brachial artery leading directly into the radial artery in which the pulse is felt By means of opening a small outlet screw on the bulb some of the air in the apparatus is allowed to escape and the pressure is lowered When this pressure falls to a point where it equals, or is slightly lower than, the highest pressure in the brachial artery, the artery opens again, blood flows to the radial artery, and the pulse reappears This pressure, called *systolic pressure*, is the pressure produced by ventricular contraction, and is equal to the resistance to stretch offered by the elastic wall of the artery as the blood is pushed against it by the ventricular systole

Another method involves the use of the *stethoscope*, the instrument used especially in examining the chest It amplifies heart and breathing sounds so that irregularities can be easily detected In this case, it is placed over the brachial artery just below the position of the arm band The bag is inflated, as in the previous method, until the pressure within it is judged to be slightly greater than the arterial pressure of the subject The pressure is then allowed to fall gradually and, by means of the stethoscope, the observer can hear a very feeble clicking sound indicating the precise moment when the blood first seeps through the artery The pressure at this point is the greater or *systolic pressure* If, now, the pressure in the bag is lowered further, at first the sounds become progressively louder, and then suddenly disappear The pressure at the time of, or just preceding, this disappearance is the lesser pressure and is known as *diastolic pressure* At this point, the ventricle is relaxed and the resulting pressure is due to the elastic recoil of the arterial wall on the blood within it during the period of ventricular diastole

The difference between systolic and diastolic pressure is called *pulse pressure* It immediately becomes apparent that this is the working pressure of the heart It represents the increase in pressure exerted by ventricular systole and is essential in keeping the blood flowing

The average normal systolic pressure of young adult male humans is about 120 mm Hg the diastolic is approximately 80 mm Hg, therefore the pulse pressure is 40 mm Hg The 3 2 1 ratio of systolic, diastolic, and pulse pressures is fairly constant

NORMAL VARIATIONS IN BLOOD PRESSURE

Blood pressure varies with age At birth the systolic pressure averages about 40 mm Hg although it may vary from 20 to 60 mm The diastolic pressure averages 20 mm However, the arterial pressure increases so rapidly that by the end of a week or two, systolic pressure averages around 70 mm and at the end of a month 80 mm Other average systolic, diastolic and pulse pressures for different age groups are presented in Table 15

TABLE 15

Arterial Blood Pressures in Humans at Different Ages
(in mm Hg)

Age in Years	*Systolic*	*Diastolic*	*Pulse*
At birth	40	20	20
1–2	85	60	25
3 4	90	65	25
10	103	70	33
15	110	70	35
20	120	80	40
30	130	85	45
40	140	90	50
50	145	90	55
60	150	90	60

Blood pressure varies according to the sex of the individual, being about 10 mm Hg lower in women than in men During sleep or relaxation the pressure is lower than otherwise, it may fall as much as 15 to 30 mm Hg pressure This is partly owing to the prone position in which less pressure is needed to pump blood to the brain and to return it from the legs

Exercise and emotional disturbances cause an increase in arterial blood pressure, the degree of rise depending upon the strenuousness of the exercise or the intensity of anger, fear, or worry

Individuals who are overweight are more apt to have high blood pressure than those of normal weight

PATHOLOGICAL VARIATIONS IN BLODD PRESSURE

Hypertension or High Blood Pressure

The blood pressure may vary from the average because of various pathological conditions It is difficult to draw a sharp line between the normal and the abnormal, but a persistently high pressure, 15 mm., or more, above the normal average systolic, is considered high blood pressure or *hyperten*

sion There are two types of hypertension (1) *primary* or *essential hypertension* which is not associated with kidney disease, but seems to be the result of a general peripheral vasoconstriction, and (2) *secondary hypertension* which is associated with kidney disease The secondary type is evidently caused by a great reduction in the vascular bed (chiefly the capillary capacity) of the kidney as the result of a narrowing of the arterioles and destruction of the capillaries of the glomeruli (the filtering units of the kidney) It is also suggested that the kidney, itself, produces a substance having a pressor effect upon the small vessels

High blood pressure is associated with hyperthyroidism lead colic and *angina pectoris*

The cause of increased peripheral resistance is not known but numerous suggestions and assumptions have been made The production of *toxic* substances having a pressor effect, hyperactivity of the sympathetic nervous system and, therefore, greater secretion of sympathin, causing increased pressure by vasoconstriction, and *arteriosclerosis*, or hardening of the arteries, not a cause but possibly a contributing factor toward high pressure, all of these have received attention as possible explanations of hypertension

Hypotension or Low Blood Pressure

A blood pressure that is persistently 10 mm Hg pressure below normal for any individual is called *hypotension* Low blood pressure is associated with many abnormal conditions some of which are tuberculosis, malnutrition, hypothyroidism, Addison's disease, hemorrhage or shock, and certain heart defects

ARTERIOLE AND CAPILLARY PRESSURES

The blood pressure falls rapidly between the point of origin of the arterioles and that of the venules The pulse wave also disappears in the arterioles, for the reasons already discussed Because of the still high hydrostatic pressure on the arteriole side of the capillaries, 30 to 50 mm Hg a great deal of filtration takes place through their walls with a very slight loss, however, of the protein content of the plasma Thus, when the blood reaches the venous end of the capillary where the hydrostatic pressure has lowered considerably (to about 15 mm Hg), its protein content is high compared with that of the plasma The blood pressure is below the protein osmotic pressure, resulting therefore, in a movement of some of the tissue fluid back into the blood stream by means of osmosis

All of the capillaries are never fully dilated at one time, a situation prevented by regulating mechanisms in the body For example, when

the capillaries of the muscle tissue are dilated as the result of exercise, those of the abdominal cavity are constricted automatically If all capillaries should expand or open at the same time, the blood would back up into the capillaries, leaving too small a residue of blood for the heart to pump

CONTROL OF THE ARTERIOLES AND CAPILLARIES

A sympathetic nerve supply to the capillaries, already described, appears to be less important than chemical control, by which means, the tonus of the walls of the capillaries and arterioles is varied A decrease in the tone, or dilation depends chiefly upon the presence of some metabolite such as histamine or a histamine like substance

The arterioles do not always pass blood on through to the capillaries In the skin regions of distal parts of the body, such as the toes, fingers, ears, and the face in general direct connections exist between arteriole and venule By means of this route the blood can pass from the arterioles to the veins without going through the capillaries These arteriole like vessels that connect arterioles and venules (in a manner similar to the capillaries) are called *anastomoses* The walls of these so called anastomoses' contain smooth muscle which is under nervous control The anastomoses, occurring only in those areas of the body concerned with heat loss, open when there is need to cool the body Thus the temperature of the skin is greater when these vessels are open than when the capillaries are fully dilated Naturally, capillaries dispense some heat but they also give color to the skin

The color and temperature of the skin, therefore, depend upon the amount of blood in the capillaries and the anastomoses between arterioles and venules

A *red warm skin* signifies the dilation of capillaries and anastomoses, a *pale warm skin*, dilation of anastomoses and constriction of capillaries, a *red cool skin*, dilation of capillaries and constriction of anastomoses, and a *pale cool skin*, constriction of both capillaries and anastomoses

VENULE AND VENOUS PRESSURES

As the capillaries join to form venules, which in turn unite to form larger veins, the area of the vascular bed is again decreased, resulting in an increase in the rate of blood flow The velocity is only about one half that in corresponding arteries, since the cross sectional area of the veins is about twice that of the arteries

Many factors influence the extremely low pressure in the veins, some of them are

1 The *force of the ventricular contraction*, considerably dissipated at this point, is, however, still slightly effective on reaching the veins

2 The *effect of gravity*, often referred to as the hydrostatic effect, is obvious The weight of the column of blood presses against the lower arterial and venous walls (the weight of a column of blood 5 ft high would exert a pressure equal to 125 mm Hg) This weight necessitates a great resistance in the lower leg vessels which are greatly contracted when one stands in an erect position Failure of the veins to counteract the hydro static effect may result in so called *varicose* veins These are veins abnormally dilated because of the failure of valves further up the leg to function, with the result that the pressure due to gravity causes the weakened vein walls to expand

3 The *massaging effect of muscular contractions* in the limbs plays an important role in the movement of the blood through the veins As explained previously (page 352), the contractions of the muscles propel the blood forward because of the structural arrangement of the valves

4 The action of the *respiratory pump* is such that blood is actually sucked up through the inferior *vena cava* at each inspiration The pressure in the thorax is always subatmospheric but at this time that of the pleural cavity tends to become even more negative Since the large *venae cavae* occur in this general area the negative pressure will naturally affect them

5 The *amount of blood* passing through the capillaries at any given moment will also influence the venous return The more rapid the flow from the arterioles through the capillaries the greater will be the pressure on the veins It is this increase in venous pressure that excites the Bainbridge reflex (page 347) by stimulation of receptors in the veins near the heart

ORIGIN OF VENOUS CONTROL

The superficial veins are contractile as might be expected from the presence in their walls of smooth muscle fibers arranged in a manner conducive to constriction The veins dilate when the skin is warmed and contract when it is cooled These contractions have been noted in a denervated area treated in this manner and may therefore be produced either by a physical stimulus or by chemical changes resulting from such a stimulus

However the smooth muscles of the veins with nerves leading to them are effective in producing dilation or constriction Nervous conduction can be demonstrated by placing an arm in cold water not only do the veins

in that arm contract but, as the result of reflex action, the veins in the other arm contract also

THE PULMONARY CIRCULATION

The right ventricle forces impure or unoxygenated blood into the pulmonary artery branching into each lung. The amount of blood leaving the right ventricle is the same as that leaving the left. An unequal flow would soon result in the blood failing to flow properly. For example, the left ventricle pumps 60 cc of blood with each beat but suppose at the same time the right ventricle should pump only 30 cc to the lungs with each beat, very soon then the left ventricle also would have only 30 cc to pump with each beat and thus would have only half the amount needed for the tissues.

The pressure of the blood in the pulmonary artery is much less than that in the aorta, being approximately 30 mm Hg. The blood is not pumped any great distance in this circuit, and the heart being on the same level as the lungs, the blood could almost flow into them even if the ventricle gave no force to it. Little is known about pulmonary, venous and capillary pressures; the capillary pressure may be 4 to 5 mm and the venous 3 to 4 mm Hg.

THE CORONARY CIRCULATION

The coronary circulation takes place within the heart. Blood enters the heart through the two coronary arteries originating behind the semilunar valves of the aorta. Most of the blood flowing into the coronary system

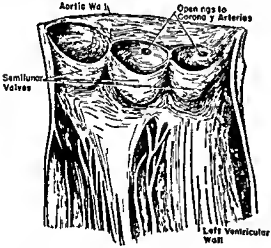


FIGURE 226

The openings into coronary arteries behind the semilunar valves

passes out into the right auricle by way of the coronary vein which empties into the coronary sinus. However, only about three fifths of the coronary blood returns to the general circulation in this manner, the remaining two fifths being returned by other vessels into the left auricle, the right ventricle

or even the left ventricle This does not appear to be so odd when we understand the conditions under which the blood flows in the coronary circuit During the contraction of the ventricles of the heart, contrary to the procedure in the systemic circuit, a lesser flow of blood takes place through the coronary system, due to the squeezing effect of the contracting ventricles on the vessels However, as soon as the ventricles begin to relax, the blood under very high pressure in the aorta, is forced into the coronary arteries At the same time, a suction action may be produced by the ventricles as they expand, that is, a negative pressure may be produced within them which could draw in blood from the veins and sinuses of the coronaries In other words, the coronary flow is least during ventricular systole and greatest during diastole It has been estimated at about 40 to 50 cc per gram of heart per hour during rest

CHEMICAL AND PHYSIOLOGICAL FACTORS IN REGULATION OF CORONARY FLOW

During asphyxiation, when insufficient supplies of oxygen are carried by the blood, the heart compensates temporarily for the decrease in two ways (1) the flow of blood through the coronary vessels is increased, (2) the percentage of oxygen abstracted from the blood by the heart muscle increases proportionately as the oxygen content decreases Thus there appears to be a natural attempt to furnish the heart muscle with its normal supply of oxygen despite the deoxygenation of the arterial blood during asphyxiation

Figure 227 shows the relation of coronary blood flow and oxygen consumption to the degree of oxygenation of the blood hemoglobin The values are taken from results obtained with a heart lung preparation When the coronary arterial blood was saturated with oxygen, the rate of flow was rather constant, at about 50 to 60 cc per minute However, as soon as the oxygen saturation is reduced by replacement with nitrogen, the rate increases, when the oxygen saturation is about 5 to 7 per cent, the rate of coronary flow increases to 250 or 300 cc per minute, decreasing again, when oxygen is supplied The amount of oxygen obtained by the heart muscle does not vary greatly, remaining on the average about 3 cc per gram per hour

PORTAL AND HEPATIC CIRCULATIONS

The vessels carrying blood to the stomach, spleen, pancreas, and intestines break up into capillaries in these organs and then reunite to form the large *portal vein* This vein transports all of the materials absorbed through the intestinal walls to the liver where the vein again breaks up into capillaries

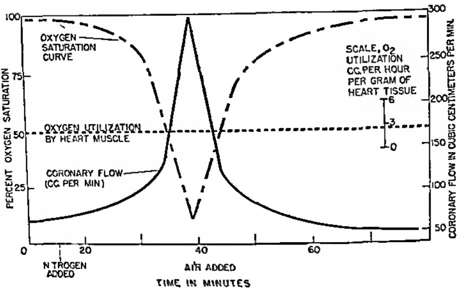


FIGURE 227

Diagram representing the flow of blood in the coronary vessels in relation to the oxygen saturation and the oxygen consumption of heart muscle Note that the oxygen utilization is quite steady even in extremely low oxygen tensions (Redrawn from Hilton and Eichboltz J *Physiol* 59 413 [1925])

In this way, the absorbed carbohydrates and amino acids are brought into direct contact with the liver cells, which act upon them There is also the *hepatic artery*, coming to the liver directly from the aorta, thus ensuring an adequate supply of oxygen for the liver cells The blood within the hepatic artery is under high pressure, whereas that in the portal system is under very low pressure Blood coming into the liver by both portal vein and hepatic artery leaves by one vessel, the *hepatic vein*

ADDITIONAL READING

Best, C H , and N B Taylor, *Physiological Basis of Medical Practice*, 5th ed (Baltimore Williams and Wilkins, 1950), chs 14, 15 Dynamics of circulation, arterial blood pressure

27

Shock and Vasomotor Activity

SHOCK

Shock may be defined as *that condition of the circulation in which there is an inadequate blood volume* Traumatic or wound shock surgical and nervous shock are fundamentally produced in the same way

One of the most obvious causes of shock is blood loss or hemorrhage, resulting from a wound or a surgical operation Although a person after a severe hemorrhage may not show many visible signs pointing to a physiological abnormality his condition nevertheless may be critical As soon as a severe blood loss occurs certain mechanisms begin to operate to compensate for the loss Further loss of blood may ultimately overtax these mechanisms and lead to their failure

Two general mechanisms by means of which the body immediately tends to overcome the effects of blood loss have been mentioned previously (page 300) (1) a reduction in the capacity of the circulatory system by vasoconstriction and by constriction of the spleen which adds several hundred cubic centimeters of fresh blood to the circulation and (2) a rapid absorption of tissue fluid replacing the lost blood volume

Should the body fail to compensate for the loss the arterial blood pressure would continue to fall resulting in an inadequate supply of oxygen to the tissues If this condition should continue for too long a period of time it might lead to serious damage especially to nerve tissue death might even result If shock appears immediately after wounding it is known as *primary shock* and if it develops more slowly that is several hours after the injury has occurred it is called *secondary* shock In either type the victim although usually sweating is cold restless thirsty with a barely perceptible pulse and considerably decreased blood pressure

Shock may appear in some cases without any apparent loss of blood for example a limb may be crushed or one may suffer severe burns without any blood loss In these cases evidently some internal change allows a great deal of plasma to escape into the tissue spaces the blood volume may be decreased dangerously in this way

Shock may be produced experimentally in mammals by (1) crushing

a limb with the animal anesthetized, (2) exposing the contents of the abdominal cavity which allows fluids to evaporate, or (3) injecting histamine

CAUSE AND TREATMENT OF SHOCK

The cause of shock is not clearly understood Seemingly, many factors contribute to its appearance, hemorrhage being only one, although certainly the most important of these

Theories have been advanced from time to time in an attempt to explain primary and secondary shock It appears certain that because of the rapid changes taking place in primary shock, there must be some nervous connection Theories based upon humoral action have also been proposed Some claims have been made that histamine or a histamine like substance, released by crushed tissues, may be a direct cause of shock It is likely that both nervous and humoral factors are involved

Whatever the original cause or causes of shock, the treatment is fundamentally the same control of hemorrhage or fluid loss, removal of damaged tissue should a toxemia be produced and the infusion of plasma or whole blood to compensate for the fluid loss

THE CONTROL OF THE BLOOD VESSELS

Claude Bernard who added so much to our knowledge of physiology, was responsible for some of the first investigations on the sympathetic control of blood vessels Although he had previously suspected this influence of the sympathetic system the results of his experiments were not published until 1851

VASOCONSTRICTION

The constriction of any blood vessel is called vasoconstriction and the mechanism concerned is chiefly under control of the sympathetic division of the autonomic nervous system Bernard the first to demonstrate vasoconstriction in one of his classic experiments cut the cervical sympathetic nerve on one side of a rabbit and found that the vessels in the ear on that side having become dilated no longer retained their normal tone He noted also that the temperature of this ear was greater than that of the opposite ear which was still innervated by the cervical sympathetic nerve The temperature increases as a result of the large amount of blood flowing through the dilated vessels Stimulation of the peripheral stump of the cut nerve causes the blood vessels of the ear to constrict presenting further proof that this sympathetic nerve is a vasoconstrictor nerve

The bilateral vasoconstrictor center of the medulla always active to a varying degree, is stimulated both directly and indirectly High carbon dioxide content of the blood has a direct action on the center, bringing about vasoconstriction (hence high blood pressure and more rapid blood flow) Low oxygen content acts chiefly upon chemoreceptors of the aorta and carotid bodies which send impulses to the vasoconstrictor center in this manner bringing about vasoconstriction reflexly

Vasoconstrictor nerves of the sympathetic division lead chiefly to the small vessels of the skin and, by way of the splanchnic nerves to those of the abdominal region The vasoconstrictor fibers located in the vagi nerves of the coronary vessels are parasympathetic

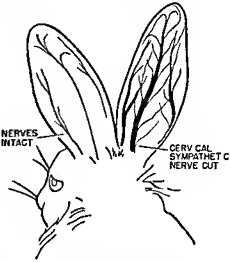


FIGURE 228

The cervical sympathetic nerves carry impulses that cause constriction of blood vessels (vasoconstriction) Cutting these nerves therefore causes the blood vessels to dilate

VASODILATION

Claude Bernard is credited also with the discovery of vasodilator nerves In an experiment on a cat he exposed the *chorda tympani* nerve a branch of the seventh cranial or facial nerve, running to the salivary glands He found that by stimulating this branch the blood vessels in the salivary glands dilated and the secretory cells produced a much greater quantity of saliva

Vasodilator centers are present in the medulla with subsidiary centers occurring in the sacral region of the spinal cord Contrary to the condition obtaining in the vasoconstrictor center these do not show tonic activity

At least three types of vasodilator nerves exist (1) *parasympathetic vasodilators* such as those for the salivary glands (*chorda tympani*) and the tongue others innervate the pelvic region and the genital organs which become engorged with blood (2) *sympathetic vasodilators* of the blood vessels of the skeletal muscles and heart and (3) *axon collateral* (*posterior root*) *vasodilators* the conduction in which is commonly referred to as antidromic conduction Branches of sensory fibers lead to blood vessels with the result that normally when the receptor from which the one branch leads is stimulated the impulse travels up the sensory neuron to the spinal cord However the impulse spreads also over the collaterals to the

blood vessels causing them to dilate This phenomenon, known as the *axon reflex*, is the shortest reflex known, since the impulse travels over but a

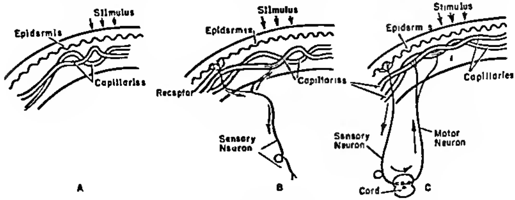


FIGURE 229

Three different ways in which vasodilation is accomplished A, direct stimulation, B, antidromic conduction and C reflexly

part of a single neuron It should be noted also that this type of conduction is the sole exception to the Bell Magendie Law (page 129).

VASOMOTOR REFLEXES

The vasoconstrictor and vasodilator fibers are grouped together as vasomotor nerves As previously described, the vasomotor mechanism regulates the amount of blood reaching an organ at a particular time The regulation must be of such an order that if any extensive vascular bed, contained within a particular organ or group of organs, has its capacity increased by dilation of arterioles and capillaries, the vessels in another region of the body must constrict correspondingly, in order to decrease the capacity of that region, and thereby maintain a normal blood pressure

This regulation is very noticeable in the vessels of the abdominal region in conjunction with those of the skeletal muscles and peripheral region The abdominal organs are gorged with blood after a meal, the vessels dilate and the blood capacity increases in that region At the same time, the capillaries and arterioles of the skeletal muscles constrict, a procedure essential for the maintenance of normal blood pressure The listless, tired and sleepy sensation often experienced after a meal may be due to the fact that the muscles are not obtaining so much blood and also that the blood flow to the brain has been decreased

The constriction of the vessels of the skeletal muscles is accomplished by parasympathetic impulses as is the dilation of the vessels of the abdominal area, which are innervated by fibers of the vagi nerves

During exercise or excitement, the sympathetic fibers come into play Their action is just the reverse of that described above, blood vessels of the abdominal area and skin are constricted, whereas those of the skeletal muscles and heart are dilated The vasoconstrictor fibers arrive at the abdominal areas by way of the splanchnic nerves which consist of three pairs of large trunks—the greater, the lesser, and the least splanchnic The fibers are formed by preganglionic fibers originating in the cord and forming sympathetic chains that pass through the lateral ganglia, in the area between the fifth and the twelfth thoracic segments inclusively, without making synapse Many of their fibers meet in the *coeliac ganglia* (collateral ganglia) where synapses are made with the postganglionic fibers leading to the viscera The coeliac ganglia are masses of nerve tissue found on the aorta just below the point where the coeliac artery leaves to supply the liver, stomach and intestines The entire mass is commonly known as the *solar plexus*

NERVOUS CONTROL OF THE VASOMOTOR CENTERS

Evidently two antagonistic types of sensory fibers so affect the vasomotor centers in the medulla that normal tonus of the blood vessels is maintained These are (1) the *depressor fibers* which when stimulated, carry impulses inhibiting the vasoconstrictor center and stimulating the vasodilator center, causing the vessels to dilate and the blood pressure to fall, and (2) the *pressor fibers* which excite the vasoconstrictor center and inhibit the vasodilator bringing about an increase in blood pressure

DEPRESSOR AND PRESSOR NERVES

Nerve fibers, originating in end organs similar to the stretch receptors of tendons and functioning as sensory depressors, are present in the walls of the arch of the aorta and of the carotid sinus The carotid sinuses are enlargements on the carotid artery at that point where it divides into external and internal carotid The receptor structures are stimulated by blood pressure in the carotid artery, and cause impulses to be conducted over the afferent nerve for the reflex (the glossopharyngeal or ninth cranial nerve) If the pressure rises, more impulses pass to the vasodilator center and excite it while simultaneously they inhibit action of the vasoconstrictor center Thus, vasodilation occurs and a decrease in the peripheral vessel resistance and the pressure tends to fall back to normal or near normal At the same time, some of the impulses get to the cardio inhibitor center which causes the heart rate to decrease Thus we have a protective device which operates

reflexly in preventing too great a rise in pressure If, on the other hand, pressure falls in the carotid sinus fewer impulses pass over the afferent nerve As a result, the vasodilator center is inhibited the vasoconstrictor center is stimulated and the cardio inhibitor center becomes less active, the net result is a rise in blood pressure

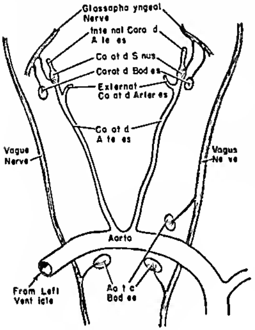


FIGURE 230

The carotid sinuses carotid bodies and aortic bodies

This mechanism is especially important to the brain since the blood vessels in the brain do not constrict or dilate to any great extent The central nervous system is contained within a rigid bony case, and therefore, cannot expand or shrink too greatly without serious damage The carotid sinus, therefore, is placed advantageously in that it guards the brain against pressure increase in the manner described It also assures an adequate blood supply to the brain and compensates for the fall in pressure taking place within the carotid artery when one stands up suddenly The delicate mechanism of this reflex thus has a part in aiding man to maintain an upright position

The effect of rise in blood pressure on the carotid sinus end organs can be shown experimentally by exposing the carotid sinus of a dog with a part of the artery and the nerves intact If Ringer s solution under high pressure is passed through the carotid sinus of the dog the pressure within the circulation falls below normal but rises again when the pressure within the sinus returns to normal

Pressor fibers occur in all afferent nerves therefore an afferent nerve if stimulated produces a rise in blood pressure Impulses are then carried to the medulla from which point they stimulate the vasoconstrictor center and inhibit the vasodilator center

CONTROL FROM HIGHER BRAIN CENTERS

The hypothalamus has some control over the vasomotor centers in the medulla and the accessory or subsidiary centers in the cord It will be recalled that the hypothalamus is the center for heat control thus the dis

covery that stimulation of the posterior hypothalamus causes vasoconstriction and increased pressure is not so surprising

It has long been known that mental excitement can influence blood pressure This may be caused in two ways either the fibers may lead from the cortex of the cerebrum directly to the vasomotor centers in the medulla or they may reach the centers by way of the hypothalamus

CHEMICAL CONTROL OF THE VESSELS

Although the carotid sinus and the walls of the aortic arch contain end organs sensitive to pressure change only, other structures nearby respond to certain chemical changes in the blood These the *carotid bodies* and the *aortic bodies* occur in close association with the carotid sinus and the aortic arch (Figure 230)

EFFECTS OF OXYGEN DEFICIENCY

Oxygen lack or deficiency in the blood stream affects the end organs of the aortic body and reflexly increases blood pressure by way of vasoconstrictor centers in the medulla This center is also affected directly by an oxygen deficiency During asphyxiation the blood pressure of an animal rises sharply, especially just before death then it drops suddenly and the animal dies The lack of oxygen reflexly causes constriction of the arterioles

Thus, by greater pressure and by more rapid blood flow, the various mechanisms attempt to obtain oxygen to compensate for the lack in the blood stream

Oxygen lack also affects the capillaries directly causing them to dilate and become filled with blood This along with the increased pressure due to extreme arteriole constriction results in an increase in the permeability of the capillary walls so that, in asphyxia the blood proteins can pass through readily At death however both capillaries and arterioles constrict forcing the blood back into the larger vessels The absence of blood in the smaller vessels causes the pallor of death

EFFECTS OF EXCESS CARBON DIOXIDE

Carbon dioxide excess has about the same end results as oxygen lack Consequently, an increase of carbon dioxide in the blood stimulates the end organs in the carotid bodies to send impulses to the vasoconstrictor and to the cardioaccelerator centers resulting in a rise in blood pressure Carbon dioxide also has a direct effect upon capillaries an excess causing dilation A sufficient increase in concentration will also cause dilation of the arterioles

It is obvious that both oxygen lack and carbon dioxide excess play a very important role in the shifting of blood into active tissues. Both conditions stimulate the centers in the medulla to produce a general arteriolar constriction, although in active areas, such as muscles during contraction, they have a direct effect on the arterioles and capillaries, producing local dilation.

The effects of carbon dioxide or oxygen can be demonstrated by means of the exposed carotid sinus with carotid bodies and nerve intact. If fluid without oxygen, or with excess carbon dioxide, an excessively acid fluid, is passed through the preparation, the blood pressure increases; conversely, if an alkaline solution is used, it decreases.

Carbon dioxide is also an important factor in respiration and will be discussed from that point of view later (page 396).

EFFECTS OF CARBON DIOXIDE DEFICIENCY

A decrease in the carbon dioxide concentration in the blood has pronounced physiological effects, the vasodilator centers being stimulated and the vasoconstrictor centers inhibited; at the same time, the cardio-inhibitory center is stimulated. Consequently, the heart rate decreases and the blood pressure falls.

Thus, in spite of the fact that we breathe to get rid of carbon dioxide, some of it is essential for a proper tonic condition of the vascular bed as a whole. This is done by means of reflexes through the medullary centers and also by direct action of carbon dioxide (or acidity) on them.

In forced, deep, rapid breathing while the body is at rest, the effects of carbon dioxide deficiency can be noted. Under these conditions, the carbon dioxide is eliminated rapidly (the oxygen tension remains about the same) and is decreased considerably in the blood stream. The blood pressure falls and the brain, depending upon proper pressure for its blood supply, may be partly deprived of it. The person concerned may become very dizzy and irrational, or may lose consciousness. Of course, this happens only when one forces his breathing in order to eliminate considerable quantities of carbon dioxide from the blood; during exercise when large amounts of carbon dioxide are produced, breathing becomes rapid, naturally, in order to get rid of the excess.

EFFECTS OF HORMONES

Two hormones are of especial interest in connection with vasomotor action. The medulla of the adrenal gland secretes the hormone adrenaline, or epinephrine, which, when added to the blood stream in small amounts

has an effect similar to that produced by sympathetic stimulation The arterioles in the abdominal organs the mucous membranes, and the skin, constrict, whereas the arterioles in the skeletal muscles, and the coronary arteries dilate The extract pituitrin, from the posterior lobe of the pituitary body, when injected into the circulation in appropriate quantity, also causes a rise in blood pressure by constriction of the arterioles of the systemic circuit However, the effect is not so pronounced as that caused by adrenalin

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Wiggers, C J , *Physiology of Shock* (Cambridge Harvard University Press 1950) Detailed consideration of shock symptoms and possible causes

carbon dioxide is produced The equation for the oxidation of glucose which is characteristic of carbohydrates, can be given as follows

$$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O$$

$$\text{since}\quad R.Q. = \frac{CO_2}{O_2} = \frac{6}{6}$$

$$R.Q. = 1{\cdot}0$$

Fats take much more oxygen per molecule for complete oxidation than do carbohydrates consequently the R.Q. is found to be much less than 1·0, usually about 0·7 For example, the fat stearin which has the formula $C_{57}H_{110}O_6$, is oxidized as follows

$$2\ \begin{array}{l} CH_2COO\,C_{17}H_{35} \\ | \\ CH_2COO\,C_{17}H_{35} \\ | \\ CH_2COO\,C_{17}H_{35} \\ \quad\text{Stearin} \end{array} + 163\,O_2 \longrightarrow 114\,CO_2 + 110\,H_2O$$

muscle chemistry, including all of the reactions involved in energy production for and during the contractions The only reaction requiring oxygen in muscle metabolism is that occurring after its contraction, that is, the oxidation of lactic acid However, since this oxidation is the final limiting factor in the metabolism of the tissue, it must take place if the tissue is to maintain its activity over a period of time

DEVELOPMENT OF RESPIRATORY SYSTEM

Plant cells respire in the same manner as animal cells, they require oxygen and must rid themselves of carbon dioxide In daylight, however, green plants appear to utilize carbon dioxide and eliminate oxygen This is due to the process of *photosynthesis* by means of which the plant manufactures carbohydrates from carbon dioxide and water by the action of sunlight on the green chlorophyll Oxygen is released and carbon dioxide utilized during the activity at such a rapid rate that the whole process overshadows the opposite exchange of these gases that takes place during respiration In other words, respiration and photosynthesis occur at the same time (during daylight) in the green plant but the latter process is most evident In the absence of light, photosynthesis does not occur and the respiratory processes are most evident

In the lower invertebrate animals, gaseous exchange is not a complex problem Amoebae and other Protozoa, and the cells of sponges, coelenterates, flatworms and round worms, exchange these gases directly with the water environment surrounding them The oxygen content of the cells is normally lower than that of the external medium with the result that there is a constant diffusion of oxygen into them Thus, as long as an animal is small enough to allow its cells to come into direct contact with the environment, there is no need for special respiratory mechanisms

In the echinoderms, since metabolic processes go on slowly, there is no need for great quantities of oxygen However, the numerous layers of cells found in these animals necessitate the transport of some oxygen by way of a water vascular system The so called respiratory tree' of sea cucumbers, a much branched outgrowth of the alimentary canal, is intermittently filled with sea water, bringing a fresh supply of oxygen with it to the inner cell layers The starfish and other members of this group also obtain oxygen through the respiratory papillae, finger like evaginations on the body surface arising from the coelomic cavity

Among the annelids are two essentially similar methods of obtaining oxygen The earthworm 'breathes' through its skin Capillaries are found in great numbers near the surface, and oxygen thus diffuses into the blood

directly through the skin Although the earthworm is an animal that lives slowly, its metabolism is much greater than that of the echinoderms In fact, the need for oxygen is sufficiently great to necessitate the presence of a respiratory pigment (an oxygen carrier) in the blood stream Some annelid worms have *gills*, special organs so densely vascular that most of the oxygen absorbed by the body finds its way into the blood stream through their capillaries

The *tracheal system* of the insects has already been mentioned (page 274) as an exceptional type of respiratory system The tubules, becoming progressively smaller as they proceed to all parts of the body, carry oxygen directly to the tissue cells, thus eliminating the need for gills or lungs However, the crustaceans (crabs lobster, and crayfish) also of the phylum Arthropoda, possess gills and have a respiratory pigment (hemocyanin) which unites with oxygen in the gills and gives it up in the tissues

The degree of vascularization of a respiratory organ seems to depend upon whether or not the animal is a 'water breather' or an 'air breather' In a comparison of land snails and slugs with water snails, one finds the highest degree of vascularization in the land animals Their moist mantle cavities are much more richly supplied with capillaries than those of the water snails, thus enabling the land snails to exchange respiratory gases more readily than the latter

Gills

The lowest classes of vertebrates breathe by means of gills In fish, the water passes into the mouth and is then forced over the gills This is accomplished partly by the alternate opening and closing of the operculum and the maxillary valve (Figure 231) The gill structure is fundamentally the same in principle as that of the lungs Many capillaries occur on the surface giving to it a brilliant red color The blood that flows into these capillaries is venous, it becomes oxygenated and in the fish passes into the dorsal aorta

Some fish breathe through their skin the 'mud hopper' of the East Indies uses its caudal fin as a respiratory organ and the eel can migrate over wide stretches of land because of its ability to absorb oxygen over most of its skin surface

The swim bladders of some fishes act as accessory organs of respiration It is thought by some that water breathing through gills is much more efficient than air breathing by means of lungs The amount of oxygen dissolved in water is much less than the oxygen in air, therefore, it was concluded that the efficiency of the gill would have to be greater since the fish

obtained all the oxygen it needed under these circumstances Actually, however, all respiration is aquatic The oxygen in the lung must dissolve in, and pass through, a relatively thick watery layer or surface film It is therefore comparable to diffusion into the capillaries of the gill

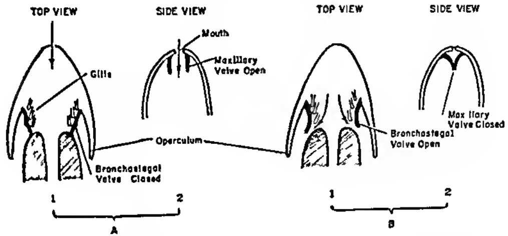


FIGURE 231

Diagrammatic representation of gill breathing in fish A bronchostegal valve closed mouth open to allow entrance of water B valve opened mouth closed to allow water to pass over gills 1 top view 2 side view

Lungs

Some fishes, because of their partial migration to land have developed saclike structures that function as lungs although these species also retain their gills The lunglike organ is the more highly developed of the two structures but, as pointed out previously fundamentally both function in the same manner Lungs are always imbedded deeply within the body of organisms because a moist surface is essential for the necessary diffusion of gases

The amphibians are excellent examples of a transformation from gills to lungs Some of them such as the mud puppy, have gills throughout life some, such as the axolotl have both lungs and gills throughout life and others such as the frog have gills in the tadpole stage but lose them during metamorphosis when lungs develop to replace them These lungs are very primitive and saclike, although more advanced than those of the lungfish Many partitions occur in the frog lung giving it more surface no bronchioles are present, however (Figure 232) Frogs and other amphibians also depend to a large extent upon interchange of gases through the skin Because of this ability some amphibians among them certain of the salamanders

can continue to live without either lungs or gills The axolotl survives after both lungs and gills are cut off In the frog about one third of the total oxygen and three fourths of the carbon dioxide exchange takes place through the skin, however, it occurs only if the skin is moist (covered with water) Thus frogs can remain under water for long periods of time but if allowed to escape into a dry room without access to water, they soon die the skin becomes dry and prevents most of the car bon dioxide from passing from the body

FIGURE 232

Lung structure in the frog

The frog takes air into the buccal cavity by way of the nares and by movement of the floor of the mouth The nares are then closed and the air is "swallowed or forced into the lungs This air, stirred well by movements back and forth from mouth to lung, can be used over and over by the frog, the valves in the nares preventing its escape in that direction

Birds have a unique respiratory mechanism Many air sacs lead from the well developed lungs into the bones and other tissue areas In addition to being a part of the respiratory system, these air sacs function also in making the birds more buoyant

The Mammalian Lung

In mammals, air passes through many structures from the nasal cavity to the functional units of the lung In the nasal cavity it must pass over the respiratory epithelium, a layer well supplied with small blood vessels that warm the air before it enters the lung The surface, exposed to the air, is made larger by means of *conchae* (Figure 123, page 207), shelflike organs partly supported by the turbinate bones Recent work has shown that not only will the respiratory epithelium warm the air but it will also cool it, if the temperature of the air is higher than that of the blood Thus dry air that enters the nose at 212 degrees F is reduced to almost body temperature, that is, about 100 degrees F by the time it reaches the lower part of the pharynx

From the pharynx, the air passes into the *larynx*, the upper part of the trachea, commonly called the voice box About twelve centimeters from the larynx the trachea branches into two *bronchi*, the right dividing into three smaller branches and the one on the left into two branches These branches divide into many smaller branches (*bronchioles*) finally forming *terminal bronchioles* leading directly into *respiratory bronchioles* which in

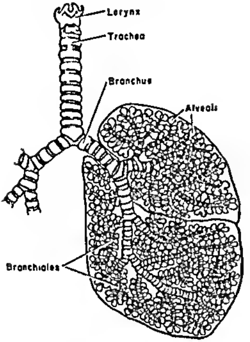


FIGURE 233

The mammalian lung and its associated structures

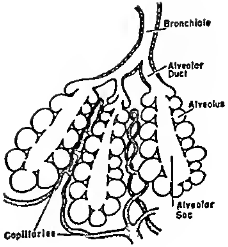


FIGURE 234

Alveoli and blood capillaries in the lung

turn, lead to the *alveolar ducts* and then to the *alveolar sacs*. A few alveoli lead off directly from the respiratory bronchioles and gaseous exchange can take place although these bronchioles function chiefly in conducting air to the alveolar ducts and sacs. The alveolar sacs are made up of many *alveoli*, the functional respiratory units of the lung. The alveolar walls, which are about 4 microns thick, permit gases to pass to and from the blood flowing in the many capillaries immediately surrounding the alveoli. It has been estimated that 750,000,000 alveoli are present in the human body. The total diffusion area in an average man is about 100 to 125 square meters, approximately fifty times that of the skin surface. During inspiration, the alveoli, the alveolar sacs and ducts, and the respiratory bronchioles dilate. The larger tubes of the lungs do not change diameter greatly because their cartilaginous walls make them rather rigid, the presence of cartilaginous rings render the trachea and bronchi more resistant to pressure. In the trachea, the rings are open at the back, evidently to allow food to pass down the esophagus, which lies directly behind the trachea, without too much interference from it. In the bronchi, however, the rings are complete. In the very small bronchi and bronchioles, cartilaginous plates take the place of the rings, no cartilage is found in the smallest bronchioles, however

Smooth muscle occurs in the walls of all air passages including the alveolar ducts. It seems to be most abundant and effective in the terminal bronchioles, where, if the bronchioles contract fully, complete constriction may

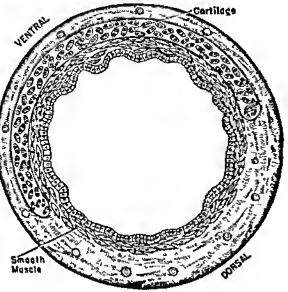


FIGURE 235

Cross section of trachea showing location of cartilaginous half rings.

occur, preventing free air passage. Ciliated epithelium lines the trachea, bronchi, and bronchioles. The effective beat of the cilia is always toward the pharynx, much foreign matter and mucus being carried out of the lungs in this manner.

The Pleural Cavity

The pleural cavity, located in the small space between the lungs and the inner thoracic walls, is lined with an elastic connective and epithelial tissue membrane, called the *pleura*. The pleura completely surrounds the lung

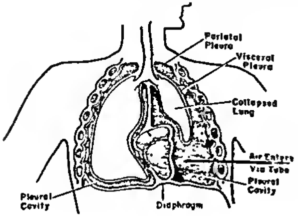


FIGURE 236

The thoracic cavity with the pleural cavity exaggerated for clarification. The left lung has been collapsed by introduction of air into the pleural cavity.

except at the entrance of the blood vessels bronchi and nerves at which point the pleura folds back on itself and lines the thoracic wall Thus it is a continuous membrane in the form of an invaginated sac That portion covering the lung is referred to as the *visceral pleura*, that attached to the thoracic wall the *parietal pleura* The space between them is extremely small and contains only a few drops of fluid that acts as a lubricant Because of the negative pressure contained therein the pleural cavity is never seen except upon closest examination However if an opening is made into the cavity the lung collapses and the cavity is more evident (Figure 236)

THE MECHANICS OF RESPIRATION

During ordinary inspiration at rest, all movements are active in that they require muscular contraction Expiration or the passage of air out of the lung however, is usually passive being simply the result of relaxation of the muscles involved in inspiration

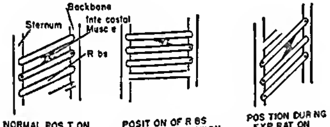


FIGURE 237

Diagram illustrating respiratory movements of ribs

Ordinary quiet breathing movements take place without one being aware of them This type of breathing is called *eupnea* and is accomplished with ease and comfort Forced or labored breathing is called *dyspnea* a person is said to be dyspneic if his breathing cannot be carried on with ease There are varying degrees of dyspnea but that appearing in individuals at rest or after mild exercise is abnormal and may be due to such conditions as heart disease anemia nephritis and respiratory diseases

Apnea meaning without breathing is a temporary cessation of breathing Although usually of short duration it may last for half a minute or even more after several minutes of forced rapid deep breathing The reason for this temporary lack of the desire to breathe will be made apparent later when the effects of carbon dioxide and other gases on breathing movements are studied Apnea is due largely to a decrease in carbon dioxide tension in the blood

Hyperpnea is an increase in the quantity of air breathed per unit time as a result of increase in depth of breathing *Polypnea* means increase in

rate of breathing These two types of breathing usually occur together They may be produced by an increase in the carbon dioxide of the blood brought about by exercise, by impulses from the cerebral cortex caused by

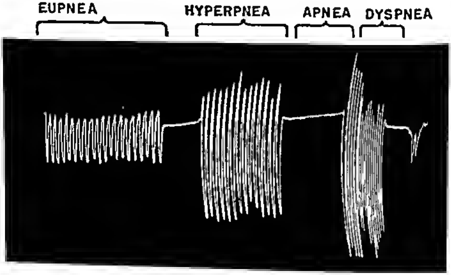


FIGURE 238

Record of various types of breathing movements Eupnea (normal), hyperpnea (deeper breathing), apnea (no breathing), dyspnea (forced breathing)

emotional upsets, or by stimulation of sensory nerves, such as those of pain, or extreme heat or cold

PERIODIC BREATHING

Periodic respiration is an uneven form of breathing and varies with different conditions The most common, *Cheyne Stokes respiration*, is characterized by a period of hyperpnea followed by one of apnea, each lasting about 30 sec Sometimes periodic breathing of this type occurs normally at high altitudes, during exercise, and in certain animals, such as the groundhog during hibernation However, it is usually the result of some serious malfunction, especially that sustained in advanced heart and renal disease, in severe pneumonia, increased intracranial pressure, and in narcotic poisoning, such as morphine poisoning It appears to be the direct result of a decrease in the sensitivity of the neurons in the respiratory center to carbon dioxide; consequently lung ventilation is reduced and the oxygen tension in the alveoli and blood decreases This oxygen deficiency acts as a stimulus to certain chemoreceptors in the circulatory vessels and finally results in a gradual increase in breathing rate and depth (Figure 239) As soon as the oxygen lack is satisfied temporarily and the carbon dioxide is

lowered to a certain level by the increased ventilation apnea follows These alternating conditions are repeated over and over

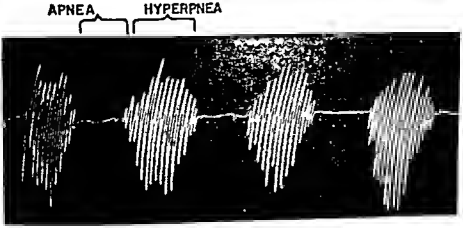


FIGURE 239

Record of Cheyne Stokes respiration (periodic respiration) A period of hyperpnea (about 35 secs) followed by a period of apnea (about 25 secs)

MOVEMENTS OF THE THORAX

At inspiration, the thorax by movements of the ribs sternum, vertebrae, and diaphragm is enlarged in three directions along its vertical, lateral, and dorsoventral planes The increase in the vertical plane is accomplished by contraction of the *diaphragm*, a strong dome shaped, muscle sheet that separates the contents of the thoracic cavity from those of the abdominal cavity When the diaphragm contracts (Figure 240) it flattens out and

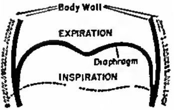


FIGURE 240

Movements of the diaphragm during expiration and inspiration

increases the capacity of the thorax Each half of the diaphragm is innervated by its corresponding phrenic nerve If one of the nerves is cut, one half of the diaphragm loses its ability to contract, and, if both are cut, it becomes entirely paralyzed, a condition usually fatal since the amount of air that can be taken into the lung without the aid of contraction of the diaphragm is inadequate

The increase in the transverse and dorsoventral direction is accomplished by movements of the ribs upward (costal breathing) The ribs increase

progressively in length from the first to the seventh inclusive, each being attached to the sternum by cartilage The eighth to the tenth ribs, inclusive, decrease in length progressively, their cartilages uniting before union with the sternum The eleventh and twelfth ribs are not attached in front and therefore are useless in respiration

Two sets of intercostal muscles connect the ribs with one another The *external intercostals* extend diagonally between the ribs, downward and forward, with the result that when they contract, the ribs are pulled upward (Figure 237, page 383), and inspiration is partly accomplished Inspiration usually involves many muscles including those of the chest, diaphragm and ribs The *internal intercostals* running in an opposite direction are covered in front by the external When they contract, the ribs are drawn downward, they, therefore are functional in expiration, although during ordinary quiet respiration they probably do not function It was pointed out above that expiration is usually a passive process in which the pull of gravity and the recoil of the tissues of the thorax play a part Muscular action enters into the process when expiration becomes forced, as in exercise and certain diseases, in which cases the internal intercostals are involved

Ordinary quiet breathing in human males is chiefly *diaphragmatic*, or *abdominal*, which, as the term suggests, simply means that the increase in the capacity of the thorax is accomplished by alternate diaphragm contraction and relaxation, at the same time the abdominal wall alternately bulges and flattens out

In the past when women were prone to wear tight fitting clothes they were forced to depend largely upon costal respiration Change of fashion and abolition of the corset allow the assumption of the more natural and efficient abdominal type of breathing However, even under normal conditions breathing is less abdominal in women than in men During pregnancy, costal respiration is much more prevalent than abdominal

THE PRESSURE CHANGES

A distinction must be made between the pressure changes in the lung *intrapulmonic pressure*, and those in the pleural or thoracic cavity, *intrapleural* or *intrathoracic pressure*

The intrapulmonic pressure can be measured rather easily by closing one nostril and inserting a rubber tube which is attached to a manometer into the other During quiet breathing a negative pressure of 2 or 3 mm Hg is registered at each inspiration and a similar positive pressure is noted for each expiration If the air passages are constricted, or obstructed in some way, these pressures may become much greater Thus in forced inspiration, the

intrapulmonic pressure is decreased to as much as —80 mm Hg a forced expiration, such as is evident in asthma, may bring about as great a pressure as +100 mm Hg

The pressure within the pleural cavity is normally always negative or subatmospheric and, for this reason the cavity is practically nonexistent The change in volume of the thorax during inspiration is owing entirely to the air that is drawn into the lung cavity

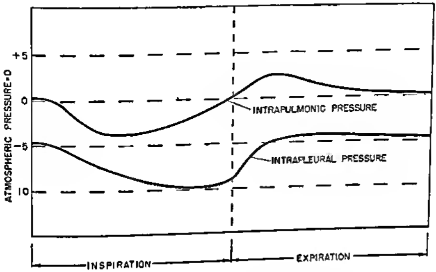


FIGURE 241

Record illustrating pressures in the lung cavity as compared to the pleural cavity and showing relationship between changes in intrapulmonic and intrapleural pressures Pressures are recorded in millimeters of mercury (atmospheric pressure is taken as zero)

To measure intrapleural pressure in a mammal, a needle connected to a manometer may be inserted carefully between the ribs through the thoracic wall into the pleural cavity During inspiration, the pressure within the pleural cavity is about —10 mm Hg and it remains negative even during expiration (about —5 mm Hg) Because of this negative pressure the lung collapses if an opening is made in the thoracic wall—a condition known as *pneumothorax* during which air fills the pleural cavity Normally, the lung is always expanded to some extent

THE ORIGIN OF THE SUBATMOSPHERIC PRESSURE IN THE PLEURAL CAVITY

Immediately following birth there is only a slight subatmospheric or negative pressure in the pleural cavity of the newborn child evidently the subatmospheric condition develops gradually

The lungs of the unborn child contain no air They are completely collapsed but, at the same time, along with the heart and other structures they fill the thorax, which does not expand until the first breath of air is taken at birth The thorax then remains expanded throughout life, and the lungs never again lose all of their air

The fact that the lungs are practically solid before birth (the spaces are not evident until after air has entered them) enables one to judge whether or not a child has died before birth The lungs of a stillborn infant will not float whereas those of one that has died after birth will float even with the heart attached This fact is utilized in legal proceedings

THE VOLUME CHANGES

The volume of the thorax increases when the external intercostal muscles and diaphragm contract and, simultaneously, the intrapleural pressure decreases still further below atmospheric pressure A truly evacuated space is never formed in this cavity, however, because the lungs fill up the space as rapidly as it tends to form Thus the negative condition is passed on to the lung cavity and consequently air rushes into the lungs At expiration the tissues return to their original state because of their elasticity, and air is forced from the lungs

With each normal inspiration and expiration, the volume of air that enters and leaves the lungs in the average adult male is equal to 500 cc, it is known as *tidal air* The lungs have a reserve capacity with the result that air can be taken into them over and above the tidal air, this is called *complemental air*, and may average around 1500 cc with greatest inspiration The volume of air that can be forced from the lung after a normal expiration is the *supplemental air* which averages about 1500 cc The sum of the tidal, complemental and supplemental air is the *vital capacity* which totals about 4500 cc in men, in women, it is about 3200 cc Some air remains in the lungs even after the most violent expiration, it amounts to about 1000 cc and is called *residual air* This, with the supplemental air, makes up the *reserve air* The residual air never leaves the lung except when the lung is collapsed, but even then some of it is caught in the alveoli by the collapse of thin walled bronchioles, this is called *minimal air*

In humans, at birth, the rate of respiration is very rapid, even at rest—between 40 and 70 times per minute With age, the rate decreases, at one year it is about 35 to 40 times per minute, at five years, about 25 times, at ten years, about 20, and at twenty five, about 16 to 18

Since the average adult during quiet respiration breathes about 16 to 18 times per minute and 500 cc of air are taken in at each inspiration, about

8000 cc of air are breathed every minute, or between 11,000 and 12,000 liters in 24 hours This volume may be increased to 70,000 cc per minute during strenuous exercise

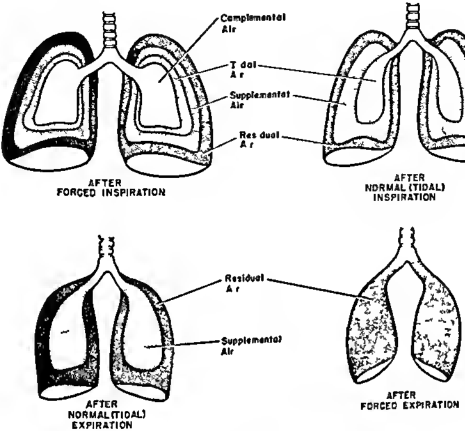


FIGURE 242

Volume changes in the lung during forced inspiration normal inspiration normal expiration and forced expiration Tidal air supplemental air and residual air are represented by different degrees of stippling

Women breathe a little more rapidly than men—about two to four more respirations per minute, but their tidal air is less, so that actually the volume breathed per 24 hours is less than that breathed by men

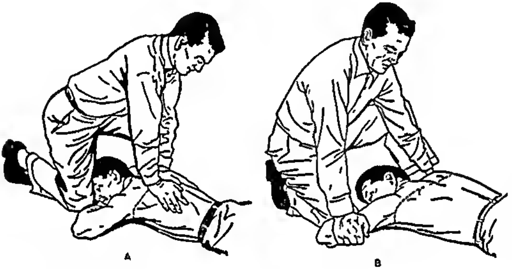
LUNG VENTILATION

The *alveolar air*, or that within the alveolar sacs and alveoli is the air physiologically important in lung ventilation The exchange of gases takes place in these small chambers It is apparent that all the air entering the lungs does not function in gaseous exchange with the blood but merely functions in filling up the accessory structures of the lungs, such as the trachea, bronchi and bronchioles This is called the *dead space air* and is equal to about 150 cc Since about 500 cc of air are taken into the lungs at

each inspiration only about 350 cc of it is actually used in ventilating the alveoli

ARTIFICIAL RESPIRATION

Sometimes in experimental work with animals, it becomes necessary to apply artificial means of respiration in order to keep them alive, also it is occasionally necessary to apply artificial respiration to humans in whom respiration has ceased because of drowning, electrical shock, asphyxiation by poisonous gases, or pressure on nerve centers in the medulla



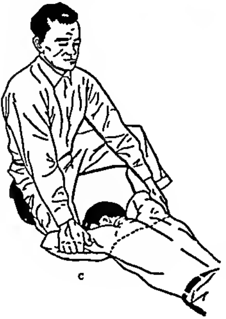


FIGURE 243

The Holger Nielsen method of artificial respiration A position of the subject and the operator during the compression phase when air is being forced from the lungs B position for the expansion phase C the expansion phase, during which the arms are drawn upward and air enters the lungs

Methods used on an experimental animal differ from those used on human beings For example, an animal that has been overanesthetized may be treated by means of a special pump A cannula leading from the pump is attached to the trachea and air is pumped into the lungs rhythmically Care must be taken to imitate the normal rate and depth of respiratory movements Too great a ventilation may rupture some of the alveoli and may be almost as injurious as too little

In humans even greater precautions are necessary Attempts should be made to rid the respiratory passages of mucus and water or any other obstruction before proceeding with the artificial respiration The so called Schaefer method was formerly employed but more recently the Holger Nielsen method has come into use The procedure for this method is to place the subject in a prone position as shown in Figure 243 with his head turned to one side The mouth should be cleared of debris and the tongue drawn forward The operator takes a position shown in the figure with his hands placed on the subject s back Air is forced from the lungs as the operator slowly rocks forward to place his weight on the subject s back Then pressure is released and the arms of the subject drawn upward toward the operator until tension at the subject s shoulders is noticed This results in air being drawn into the lungs by expansion of the thoracic cavity The subject s arms are then dropped and the entire cycle is repeated at a rate of about twelve times per minute

ADDITIONAL READING

Fulton J F *Textbook of Physiology* 16th ed (Saunders 1950) ch 39 Mechanics of respiration

Krogh A *The Comparative Physiology of Respiratory Mechanisms* (Philadelphia University of Pennsylvania Press 1941) chs 4 5 6 8 Respiratory function of vertebrates and invertebrates

29

The Regulation of Breathing Movements

THE BODY has several means by which the rate and depth of respiration may be controlled involuntarily It is common knowledge that one can also control the rate and depth of breathing voluntarily However the breath can be held for only a limited time after that one must inhale again in spite of all efforts to keep from doing so Obviously one cannot commit suicide in this manner since some mechanism actually forces the contraction of the rib muscles and diaphragm so that breathing movements occur involuntarily This mechanism consists of the stimulation by carbon dioxide of the breathing centers in the medulla so that nerve impulses are carried over the nerves leading to the rib muscles (intercostal muscles) and diaphragm

Both voluntary and involuntary movements are important the former are essential in speech and other higher human activities whereas the latter are essential to proper oxygenation of the blood Control is through the central nervous system as might be expected Since the muscles of the diaphragm and ribs are striated and are innervated by way of the central nervous system regulation must be a function of one of the higher brain centers

THE HERING BREUER OR LUNG REFLEXES

Very powerful reflex regulation of respiratory movements is the result of impulses arising in the lungs themselves hence the term *lung reflexes* which were discovered about eighty years ago by Hering and Breuer

In the lungs are receptors which are stimulated by stretching Therefore while the lungs are being inflated by inspired air these receptors are stimulated to a progressively greater extent that is the rate of impulse discharge over their sensory nerves (vagal sensory) leading from the lungs increases as the inflation increases This action is similar to that which stimulates the muscle spindles of striated muscles so essential in maintaining normal posture

The effect on the respiratory center in the medulla is first to diminish, and then halt entirely, inspiratory activity of the respiratory muscles. In this way, the lungs are protected against damage from too great an inflation. At the moment inspiration ceases, expiration begins and the number of

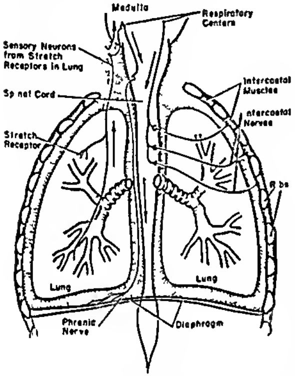


FIGURE 244

The lung reflexes (Hering Breuer reflexes). The arrows represent the direction of flow of impulses from the receptors to medulla to diaphragm and rib muscles.

inhibitory impulses coming from the stretch receptors of the lungs is diminished until eventually inspiration is again initiated. The role of chemical factors in contributing to rhythmic respiration is considered later (page 394).

If the vagal branches leading from the lungs are cut, the Hering Breuer reflexes are abolished. An animal in this condition shows very deep and slow breathing movements. Since the sensory impulses from the stretch receptors do not get through to the brain center, the lungs continue to inflate until they contain an amount well beyond their normal volume of complemental air. However, other factors present act to bring about expiration.

THE CAROTID SINUS REFLEX

Because of the phenomenon known as the *carotid sinus reflex*, the blood pressure is controlled (lowered). It has already been pointed out that stretch receptors occur in the walls of the carotid sinuses. When these end organs are stimulated by an increase in blood pressure, impulses are trans

mitted to the vasomotor and the cardio inhibitory centers in the medulla, causing a dilation of smaller vessels and a slowing of the heart rate respectively This is called the *carotid sinus reflex* and because of it, the blood pressure is lowered

The respiratory centers are also affected by impulses from the carotid sinus receptors, the depth of inspiration being diminished by an increase in blood pressure

One can prove by exposing one of the sinuses of a dog with its nerve supply intact that the carotid sinus functions in this manner The pressure in this sinus can then be varied at will by passing fluid through it under greater or lesser pressure, although the pressure remains constant and normal in the rest of the body If the pressure is increased by this method, the respiratory movements become very slow and shallow and may cease for a few seconds

The value of this reflex is not entirely clear but the evidence seems to indicate that as the blood retains more and more of its carbon dioxide if its excretion has been retarded by some means, the capillaries tend to dilate because of the direct effect this gas has on them Blood pressure is lowered by the dilation, consequently, through the carotid sinus reflex respiration is stimulated However, the carotid sinus reflex seemingly has only a very slight effect upon respiration under normal physiological conditions

CHEMICAL CONTROL OF RESPIRATION

During sleep or unconsciousness, such as in fainting, our breathing movements continue and as already pointed out, even when voluntary attempts are made to restrain these movements involuntary regulation forces the inspiratory muscles to contract As noted previously, the centers for respiratory control must lie in the central nervous system, it is now known that these centers located in the *medulla oblongata*, consist of functionally integrated groups of neurons, in which the nerve impulses leading to the respiratory muscles have their origin These neurons are stimulated by carbon dioxide the number of impulses depending upon the concentration of carbon dioxide at the center

The approximate location of the centers may be proved by destroying the brain of a mammal, little by little, beginning at the anterior end It is found that respiration is not abolished until after the medulla is destroyed Normally, some impulses pass from the centers in the medulla, over the twelve thoracic spinal nerves to the intercostal muscles, others pass over the phrenic nerves to the diaphragm

These centers can develop rhythms of their own They are not dependent

upon afferent impulses by way of lung receptor or carotid sinus, but respond to direct chemical stimulation.

The respiratory rhythm persists even in the head of a dog which has been kept alive after decapitation by perfusing through the blood vessels in its head, blood from another animal. It is commonly known that the nostrils of most mammals open and close along with inspiration and expiration respectively. In the head, treated as described, rhythmical movements of the nostrils occur, indicating that some substance in the perfused blood is affecting the centers of the medulla.

Also chemical receptors stimulated by low oxygen pressure, high carbon dioxide pressure, or acidity, are present in the carotid and the aortic bodies.

CHEMICAL CONTROL BY CARBON DIOXIDE

Obviously, the respiratory centers can be stimulated directly either by their own metabolic products or by products carried to them by the blood. The products brought by the blood could have their effect by diffusion into the brain tissue.

It is likely that in the normal resting body the carbon dioxide produced by the brain cells themselves is responsible for stimulation. The sequence of events in the regulation of respiration is as follows: carbon dioxide is produced in all active cells of the body including those of the respiratory centers. Since some of this gas is already in the blood stream, a greater concentration of it would be necessary in the respiratory center before the gas could diffuse into the blood stream. If respiration ceases momentarily as it does after each expiration, the carbon dioxide content of the blood tends to increase because it cannot escape through the lungs. At the same time the carbon dioxide produced in the respiratory centers will tend to concentrate there to the same degree as in the blood stream. Consequently because of the great sensitivity of these medullary cells to carbon dioxide they are stimulated and transmit impulses to the muscles of inspiration. At the succeeding expiration the excess carbon dioxide is carried out and there is momentarily another short period during which respiration ceases, until again there is an increase in the concentration of carbon dioxide. It has been mentioned already that impulses coming from stretch receptors of the lungs control the depth of inspiration. Together these factors assure a rhythmic respiratory rate of proper normal depth.

During exercise, such great quantities of carbon dioxide are produced that much of it diffuses into the medullary tissue. The excess increases the volleys of impulses leading from the centers to the respiratory muscles re-

sulting in an increase in respiration rate and depth. Also, if a person is made to breathe air with high carbon dioxide tension (pressure or concentration), the breathing movements increase.

ACTION OF CARBON DIOXIDE

There has been much controversy over the question as to how carbon dioxide stimulates the neurons. Some have claimed that it has its effect by virtue of the increased acidity it imparts to the fluids in which it dissolves. This view assumes that hydrogen ions are the means by which the respiratory cells are stimulated directly. Carbonic acid which is formed when carbon dioxide dissolves in water dissociates slowly into hydrogen ions and bicarbonate ions. Also, an increase in the acidity of the blood by the addition of lactic acid is associated with an increase in respiratory movements. However, it is somewhat confusing to find that lactic acid, although stronger, is less effective than carbonic acid.

The more recent evidence is in favor of the view that carbon dioxide has a direct action on these sensitive cells of the medulla. At least, it is probable that carbon dioxide diffuses into the cells, which are more permeable to it than to hydrogen ions. Thus, if it does have its effect indirectly by producing hydrogen ions, according to this view it does so within the cell.

The rate of blood flow through the vessels of the medulla influences respiratory movements. If the blood flows slowly, carbon dioxide accumulates in the tissue and respiration increases, whereas, if the blood flows rapidly, the carbon dioxide is removed rapidly and respiration becomes slower.

Cerebral blood vessels are sensitive to an excess of carbon dioxide, dilating although not extensively, with an increase in carbon dioxide tension. This dilation may be an explanation for the so-called "second wind" of athletes who suffer from respiratory distress during a contest and then find suddenly, as they continue to exert themselves, that the difficulty seems to disappear. The carbon dioxide concentration in the blood, increasing at first, has a direct action on the cerebral vessels, with the result that the blood flow through the central area is increased by their dilation, and, thus, more carbon dioxide may be carried away from that area.

CHEMICAL CONTROL BY OXYGEN DEFICIENCY

The carotid bodies and the aortic bodies contain chemoreceptors, and the function of both in the control of circulation has already been discussed. However, they also play a very important role in the control of respiration.

The increase in the rate and depth of respiration at high altitudes is well

known It occurs in spite of the decrease of carbon dioxide tension of the blood which is enhanced by the overventilation of the lungs At sea level, if one should force himself to breathe as rapidly as he breathes at high altitudes, he would become dizzy and might actually lose consciousness momentarily This overventilation clears the lungs of a large part of their carbon dioxide and, consequently, a rapid diffusion of carbon dioxide from the blood occurs, which, in turn, affects the respiratory center and lowers the blood pressure

It is obvious, then, that the increase in breathing movements at high altitudes cannot be caused by an accumulation of carbon dioxide in the blood However, chemoreceptors of the carotid and aortic bodies are sensitive to low oxygen tensions, the former bodies, especially, are instrumental in influencing respiratory movements At sea level the tension of oxygen in the lung alveoli is equal to about 100 mm Hg pressure, at an altitude of 8000 ft the tension decreases to about 65 mm At the same time the lung ventilation (liters of air per minute) increases from 7 6 liters at sea level to 8 6 liters at 8000 ft Evidently, as the oxygen decreases, sensory impulses via the glossopharyngeal nerves pass to the respiratory centers of the medulla and cause an increase in depth and rate of respiratory movements If the nerves leading from the carotid bodies in a mammal are cut, the animal can be deprived of oxygen to the point of asphyxiation, and even death, with very little effect on respiration Most evidence indicates that the chemoreceptors of the aortic body are of very little significance as compared with those of the carotid bodies

Tissue fluid, to supply the oxygen needed by the tissues, should have an oxygen tension of about 25 mm Hg This varies, depending on the activity of the tissue In order to maintain this concentration in the tissues, the blood carries about 19 cc oxygen per 100 cc This is acquired from the air of the alveoli of the lungs, which have an oxygen tension of about 100 mm If the blood does not furnish the needed oxygen to the tissues, or if the tissues cannot utilize that brought to them, a condition of anoxia is produced

fail to use the oxygen delivered to them by the blood stream In the first three types a low oxygen tension exists in the capillaries—a condition known as *anoxemia* In the histotoxic type however a normal supply of oxygen is present in the capillaries but the tissue cells are unable to use it

CYANOSIS

Sometimes a bluish coloration is associated with anoxia of the anoxic and stagnant types This is called *cyanosis* and is the result of a condition of the blood that causes a rather diffuse dusky blue color to be imparted to the skin The bluish color first makes its appearance beneath the finger nails and on the ear lobes and lips The presence of *reduced hemoglobin* (hemoglobin from which oxygen has been removed) above a certain definite amount in the capillaries produces this condition (reduced hemoglobin has a purplish color which imparts a bluish tint to the skin as it passes through the capillaries on the contrary oxyhemoglobin is scarlet in color) If oxidized hemoglobin has been dissociated to the extent that there are 5 g or more of reduced hemoglobin per 100 cc of blood in the capillaries cyanosis appears This is about one third of the total hemoglobin of normal blood However cyanosis would never appear in some types of anemia because the hemoglobin content is less than 5 g per 100 cc and therefore all of it could be reduced in the capillaries but the resulting concentration of reduced hemoglobin would be less than the essential *absolute* amount (5 g per 100 cc) On the other hand there are conditions in which the blood may have a hemoglobin concentration 100 per cent above normal or approximately 30 g per 100 cc Thus 25 g of this hemoglobin could be completely saturated with oxygen yet cyanosis would appear because 5 g per 100 cc was in the reduced state

ANOXIC ANOXIA

Anoxic anoxia is frequently due to a *low oxygen tension of inspired air* In this type of anoxia the oxygenation of the blood in the lungs is reduced and may be brought about in several ways The oxygen tension of the inspired air may be low—a condition that may exist even though the barometric pressure is normal Other gases may replace the oxygen as sometimes occurs in coal mines where the oxygen of the air may be found in lowered concentration and methane (fire damp) or nitrogen and carbon dioxide (black damp) take its place

Usually however we think of anoxia in relation to high altitudes especially in reference to aviation The percentage of oxygen at high altitudes is no different from that at sea level—approximately 21 per cent of

the air. The difference is in the total barometric pressure which decreases with altitude. For example, at sea level, the average barometric pressure is 760 mm. Hg of which 159.6 mm. is due to oxygen pressure, at 7000 ft. the barometric pressure is 586 mm. and the oxygen partial pressure, 123 mm., at 14,500 ft., it is 438 mm. and oxygen is 92 mm., at 25,000 ft. it is 282 mm., and the oxygen pressure is 60 mm.

It has been known for many years that so called "mountain sickness" is caused by a low oxygen pressure or tension in the atmosphere and not to low barometric pressure. The first signs of mountain sickness in a healthy individual usually appear between 8000 and 12,000 ft., very few symptoms being evident below 12,000 ft. Much greater variation occurs than is indicated by these figures, since a great deal depends upon the rapidity with which one ascends a mountain and upon the muscular effort put forth.

In 1876, three French scientists, in a balloon, made one of the first recorded high altitude ascents. They reached a height of over 26,000 ft. but the flight ended tragically, only one of them, Tissandier, living to tell the story. The scientists had realized the need for extra oxygen and had carried containers with them. However, they waited until too great a height was reached before they attempted to use the oxygen. By this time severe anoxia had already set in and Tissandier reported that they were unable to raise the mouthpieces to their lips. They lost consciousness at about 25,000 ft. Tissandier regained consciousness as the balloon was descending rapidly only to find his two fellow passengers dead.

A height from 20,000 to 25,000 ft. seems to be the limit to which man can ascend unless extra oxygen is supplied. Convulsions, unconsciousness, and death may follow within 3 min. at 25,000 ft. and within 15 min. at 20,000 ft., at 40,000 ft., the time reserve is less than 1 min.

SIGNS AND SYMPTOMS OF ANOXIA

Individuals exhibit a variety of symptoms and signs when ascending to high altitudes, or when suffering from anoxia. Rapid ascents in airplanes or balloons result in unconsciousness unless oxygen is inhaled. Ascent to a lesser altitude (15,000 to 20,000 ft.) may bring about in an individual reactions akin to those of drunkenness. Sensations of exhilaration and general well being may be experienced, also a definite mental and sensory dullness, along with dizziness, muscular weakness, headache, dyspnea, nausea and vomiting and a marked cyanosis. The symptoms are less evident if one climbs to high altitudes slowly, thus man can, in this way, adjust himself to the rare atmosphere. However muscular coordination and mental tasks are less efficiently carried out at high altitudes.

At sea level, the barometric pressure is equal to 760 mm Hg and oxygen which makes up 21 per cent of the air (and therefore 21 per cent of the pressure), accounts for 159 mm the alveoli of the lungs then contain oxygen at a partial pressure of about 100 mm At 18 000 ft, the oxygen still accounts for 21 per cent of the pressure but because of the rareness of

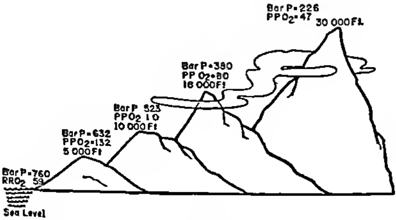


FIGURE 245

Barometric pressures and related oxygen pressures (in mm Hg) at various altitudes Bar P barometric pressure P P O_2 partial pressure of oxygen

the air at this height the oxygen tension is equivalent to about 50 per cent of the oxygen at sea level or about 80 mm partial pressure The oxygen tension in the alveolar air at this altitude is around 50 mm, and the arterial blood is less than 80 per cent saturated consequently, greater lung ventilation is necessary The lowered oxygen tension in the blood has an effect on the aortic and carotid bodies which send impulses to the respiratory center and thus indirectly causes greater respiratory movements

If one makes ascents to high altitudes very slowly over a period of several weeks or months one becomes adjusted to the rarity of the air Some immediate adjustment by contraction of the spleen takes place and an increase in heart rate, but this is coupled with a delayed adjustment in which there is an increased production of erythrocytes to as many as 9 000 000 per cu mm Natives of mountainous regions living at 14 000 to 15 000 ft have a normal blood count around 8 000 000 Thus, the hemoglobin content is increased and the total oxygen content of the arterial blood as well in spite of the low oxygen pressure

AIR EMBOLISM

Air embolism is not a condition of anoxia but may occur at the same time as anoxia because of a too rapid ascent in an airplane or balloon It

is sometimes referred to as the bends or caisson disease, because it has hitherto mainly occurred in divers and in workers in caissons, they may go too rapidly from the high barometric pressure of the caisson (2 to 4 atmospheres) to normal sea level pressure

In diving or in caisson work an increase of 1 atmospheric pressure takes place for every 34 ft of water Therefore, a person who has reached a depth of 34 ft in water experiences a pressure of 1520 mm Hg The amount of the gases in the blood plasma increases in proportion to the partial pressure of each gas, just as they would do in water Carbon dioxide is dissolved in soda water by this principle, it is forced in, under high pressure, and the cap of the bottle prevents its escape If the cap is removed and the pressure immediately over the soda water thereby reduced, bubbles of carbon dioxide form within the liquid some of them rising to the surface and escaping This is the same fundamental principle by means of which air emboli are formed in the blood stream Very high pressures may be tolerated by living systems without any harmful experiences but it is dangerous to lower the pressures too rapidly If a person is exposed to pure oxygen at 760 mm pressure there is no great increase in oxygen content of the blood At sea level and in ordinary air the hemoglobin of human blood carries about 19 cc of oxygen per 100 cc of blood it is not completely saturated The plasma carries about 0 3 cc or in all, around 19 3 cc of oxygen are carried in 100 cc of blood

In pure oxygen at 760 mm pressure, hemoglobin carries approximately 20 cc of oxygen per 100 cc of blood (its limit), whereas plasma has 2 cc per 100 cc dissolved in it, altogether, a concentration of 22 cc per 100 cc blood Under increased atmospheric pressure enough oxygen may dissolve in the plasma to make a person quite independent of his hemoglobin He may thus survive an otherwise fatal carbon monoxide poisoning in which hemoglobin is no longer free to combine with oxygen

Gases which have been dissolved in the plasma under high pressure, do not escape rapidly enough via the lungs when the pressure is lowered suddenly, they form air bubbles or emboli in the blood stream The symptoms of this condition are itching of the skin, dizziness, dyspnea, joint pains, and nausea The symptoms vary in individuals apparently depending upon the part of the body affected by their enlodgement Frothing of the blood in the capillaries interferes with circulation

The condition appears in aviators who ascend too rapidly from normal pressure to that at 25 000 to 30 000 ft, at which height the pressure is only one third that at sea level The rapid reduction in pressure does not allow sufficient time for the gases to escape by way of the lungs

Less rapid ascents in planes, and a gradual decompression in those working under high pressures, will prevent air embolism. A second cause of anoxic anoxia may be *defective or abnormal respiratory mechanisms.* Any condition lowering the amount of oxygen available to the blood passing through the lungs would produce anoxia of the anoxic type. Thus respiratory diseases, obstruction of the respiratory tubes in any way, and defective nervous and muscular control of the respiratory muscles contribute to this condition.

In *pneumonia*, the alveoli are so filled with mucus, that oxygen contact with their membranes is much reduced. As a result of this, the saturation of the blood with oxygen may be as low as 85 per cent or less, and the symptoms of anoxemia, such as cyanosis, dyspnea, and delirium, make their appearance.

A spasm of the smooth muscles of the bronchioles causes an oxygen lack or deficiency in asthma. Thus the alveoli are poorly ventilated; carbon dioxide is retained in the blood and a lowered oxygen saturation and gaseous acidosis results. This, however, is a stimulus to greater acid excretion by way of the kidney.

One suffering from asthma may experience difficulty in both inspiration and expiration but chiefly in expiration. This is thought to be due to the fact that even normally a constriction of the bronchioles occurs during expiration, although they dilate normally at inspiration. The spasm may be of a reflex nature or, more commonly, may be the result of sensitization to some foreign protein. Feathers of various birds, dog hair, pollens, or foods may constitute the foreign protein.

Failure of foramen ovale to close is also a condition producing an anoxic type of anoxia. It differs from the others mentioned, in that the blood which goes to the lungs may be fully oxygenated, but if the *foramen ovale* between the two auricles does not close at birth, some venous blood passes directly to the left auricle and mixes with the oxygenated blood. The blood is, therefore, never sufficiently oxygenated. The symptoms of anoxia are always present in individuals suffering from this condition.

ANEMIC ANOXIA

Anemic anoxia occurs when the oxygen-carrying power of the blood is reduced. Therefore, it makes its appearance in several ways. First of all, there may be an actual *reduction in the number of erythrocytes* per unit volume, such as occurs in anemia or hemorrhage. There may also be a *decrease in the quantity of hemoglobin per red cell*, although the normal number of cells is present. *Carbon monoxide*, also, reduces the oxygen-

carrying power in that it combines much more readily and more firmly with hemoglobin than does oxygen *Nitrites* and *chlorates* result in the formation of methemoglobin which is of no value as an oxygen acceptor

STAGNANT ANOXIA

A reduction in the circulation, from whatever cause, will result in the development of anoxia The slower movement of the blood and its longer stay in the capillaries is conducive to greater oxygen loss in the tissues The anoxia produced in this manner is referred to as *stagnant anoxia,* occurring in heart failure, surgical shock, venous obstruction, and valvular leakages

The hemoglobin of the arterial blood may be saturated, that is, it may carry its normal load under normal tension, but, because of the increased oxygen dissociation and utilization, much of it is reduced and often to the point where cyanosis appears Thus, the first tissues reached receive an adequate supply of oxygen but, as the blood flows on, the more remote tissues suffer from oxygen lack

HISTOTOXIC ANOXIA

In histotoxic anoxia the circulation may be normal and the hemoglobin of the arteries and capillaries, as well as the veins, may be saturated with oxygen but the cells of the body are unable to utilize it This type of anoxia occurs in alcohol, narcotics, and cyanide poisoning, certain oxidative enzymes within the cells being removed from action Cyanides affect the cellular enzyme, cytochrome oxidase, which then cannot utilize oxygen and, therefore, the cells take none from the blood stream

ADDITIONAL READING

Barcroft, J , *The Respiratory Function of the Blood* (New York Cambridge University Press, 1925), Part I, 'Lessons from High Altitudes" Personal experiences of effect of high altitude

Gray, J S , *Pulmonary Ventilation and Its Physiological Regulation* (Springfield Charles C Thomas, 1950)

Henderson, Y , *Adventures in Respiration* (Baltimore Williams and Wilkins, 1938). Discussions of various types of anoxia

30

The Chemistry and Physics of Respiration

ONCE AIR IS BREATHED, several changes take place in it its temperature is changed to equal body temperature, it becomes saturated with water vapor at that temperature, and its chemical composition is altered by the loss of some of its oxygen and the addition of carbon dioxide

CHANGES IN TEMPERATURE

The inspired air is usually cooler than body temperature (37 degrees C), although the opposite is the case for a few days (variable in number) during the hot summer months It should be noted, however, that the respiratory epithelium of the nasal cavity is as efficient at cooling hot air as it is at heating cold air The lungs, therefore, are contacted only by air at or near body temperature, a fact strikingly demonstrated in recent tests to determine how much heat the human body can stand This problem is one in which the jet plane makers are interested since speed may be so great that friction will heat the cabins to an extremely high temperature Experiments show that even at temperatures above the boiling point of water, the inspired air is cooled almost to body temperature by the time it reaches the back of the pharynx

CHANGES IN WATER VAPOR

Air taken into the lungs is very rarely completely saturated with water vapor, whereas the expired air is saturated at body temperature, that is the warmer the air, the greater the amount of water vapor required for saturation Warm air holds much more water vapor, therefore, than air at a lower temperature This may be demonstrated by blowing the breath on a cool surface, such as a mirror or shiny metal plate As soon as the air is cooled by the glass or metal the water vapor condenses This illustrates one means the body employs for getting rid of water The actual amount excreted by the lungs depends upon the degree of saturation of the inspired air, the cooler and drier this is, the more water it will gain and carry to the outside In 24 hours, an average of 350 cc of water is excreted

by the adult lung at normal room temperature (21 degrees C) and humidity

CHANGES IN CHEMICAL COMPOSITION

Changes in chemical composition are the most important in expired air The contents of pure air when completely dried as compared with those of expired air and alveolar air are presented in Table 16 The oxygen content of the alveolar air is lower than that of the expired air because the expired air contains also air from the trachea and bronchi (dead space air) from which oxygen has not been removed

TABLE 16

Percentages of Dried Gases in Breathed Air

Gas	Inspired Air	Alveolar Air	Expired Air
Oxygen	20 96	14 2	16 3
Nitrogen	79 00	80 3	79 7
Carbon dioxide	0 04	5 5	4 0

An approximate average of the oxygen utilized in 24 hours is 432 liters and the amount of carbon dioxide given off is about 380 liters The respiratory quotient is, therefore, about 0 85 to 0 88 The difference in volumes of oxygen and carbon dioxide is because of the fact that proteins, or fats, or both are being oxidized along with carbohydrates in the mammalian body If only carbohydrates were oxidized there would be no difference, and the respiratory quotient would be 1 0

IMPORTANCE OF VENTILATION

In a closed room a greater danger of depleting the oxygen supply exists than in the open air, but even in a closed room long before oxygen depletion is noticeable other important changes begin to show their ill effects These ill effects are caused by heat and moisture, both of which are given off by the bodies of humans, and if a number of persons occupy a small unventilated room at the same time, the humidity and temperature increase rapidly

Tests show that subjects placed in air tight rooms without any ventilation whatsoever, began after several hours to experience ill effects, from which they were not relieved even when allowed to breathe oxygen from the outside by means of a tube stuck through the wall On the other hand if a person on the outside breathes oxygen from inside the room through the tubes, he experiences no discomfort Those on the inside were suf

fering not from oxygen lack but from too great a humidity and too high a temperature

Modern ventilation engineering is, therefore, concerned chiefly with the temperature and humidity factors, although oxygen depletion and carbon dioxide accumulation are also considered

EXCHANGE OF GASES

Gases are exchanged in the lungs and in the tissues In the alveoli the oxygen tension which is about 100 mm Hg pressure, is high compared with that of the blood in the capillaries whereas the concentration of carbon dioxide is much greater in the blood than in the alveoli Therefore the oxygen diffuses from the alveoli into the blood and carbon dioxide diffuses from the blood into the alveoli The reverse occurs in the tissues The greater the difference in concentrations of gases in the alveoli and the blood, and of the blood and the tissues, the greater will be the diffusion of gases back and forth

In coursing through the lungs, the blood becoming oxygenated takes on a more brilliant scarlet color and is carried to the left side of the heart by pulmonary veins the only veins that carry fully oxygenated blood This change in color is due to the union of hemoglobin of the red corpuscles with oxygen to form oxy*hemoglobin*, which is carried to the tissues where it dissociates as oxygen and *reduced hemoglobin* It should be noted that in both cases the iron in the hemoglobin molecule remains in the reduced or ferrous, condition Sometimes because of action of certain substances with hemoglobin a more stable oxidized form is produced in which the iron is actually converted to the ferric state It is called *methemoglobin* and does not give up its oxygen readily Methemoglobin does not exist normally in the blood but the addition of an excess of such substances as acetanilid, or nitrites, to blood will result in its formation As already pointed out, the blood, at sea level can carry 19 3 cc of oxygen per 100 cc, 19 cc of this being carried by the hemoglobin If the corpuscles were not present, the plasma would carry only slightly more than 0 5 cc oxygen

LAWS GOVERNING DIFFUSION AND SOLUTION OF GASES

There are several so-called gas laws that should be understood in order to grasp the full significance of gaseous exchange in the body These laws are based upon the *kinetic theory of gases* which postulates the constant movement of molecules, varying directly with the temperature This motion develops pressure and brings about a uniform distribution of the gas by diffusion Three of these laws are of importance here

Henry's law, simply stated, means that with constant temperature, the quantity of gas that will dissolve in a solution, is proportional to the partial pressure of the gas When equilibrium is reached the pressure of the gas in the liquid will be approximately the same as that above it Thus, when the oxygen pressure in the alveoli of the lungs is 100 mm Hg it exerts approximately the same pressure in the blood plasma of the capillaries surrounding the alveoli

Boyle's law states that, other things being equal, the volume of a gas varies directly as the temperature Everyone has observed that gases pass out of water as it is heated to the boiling point When heated the gas dissolved in the water expands and forms bubbles which are released at the surface

Dalton's law of partial pressures states that any gas in a mixture, such as air, will exert the same pressure it would exert if other gases were not present In other words, each gas in a mixture exerts only a fraction of the pressure, this fraction is the partial pressure for that gas For example, oxygen, which makes up approximately 20 96 per cent of air, therefore at 760 mm atmospheric pressure exerts a partial pressure of about 159 mm, nitrogen which makes up 79 per cent, a partial pressure of 600 mm, and carbon dioxide which constitutes 0 04 per cent, a partial pressure of 0 3 mm

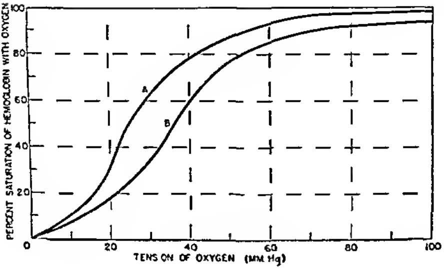
THE ABSORPTION OF OXYGEN BY THE BLOOD

As already pointed out, in animals oxygen because of its union with hemoglobin or some other oxygen carrier, is absorbed in large quantities by the blood The efficiency of the blood, as a transport agent, depends upon its ability to carry oxygen to the tissues and to carry carbon dioxide and other wastes from the tissues The oxygen must be given up just as readily as it is absorbed if it is to be of value to the body cells

The ability of the blood of different animals to carry out this function varies greatly Evidently the variation is due to the difference in the oxygen carriers or *respiratory pigments*, as they are called since all of them are colored, although the color seems to have no particular importance As far as we are aware, there is no reason why a colorless oxygen carrier would not work just as well

The efficiency of blood as an oxygen carrier is illustrated in Figure 246 This is an oxygen dissociation (or combination) curve of human blood, showing the rapidity with which oxygen is released by hemoglobin when the oxygen tension of the surrounding environment is below 50 mm Hg

The blood is seldom 100 per cent saturated Usually in the capillaries of the lungs it is 95 to 97 per cent saturated The pressure of oxygen in the


PERCENT SATURATION OF HEMOGLOBIN WITH OXYGEN
100
80
60
40
20
0
A
B
20
40
60
80
100
TENSION OF OXYGEN (MM Hg)

The loading and unloading tensions vary in different bloods, being greatest for mammalian blood

THE RESPIRATORY PIGMENTS

There are at least five different types of respiratory pigments found in the transport media of animals They all fulfill the essential requirement of an efficient oxygen carrier—the ability to react reversibly with oxygen The loading tensions are equal to or less than the oxygen tension of the environments of the animal (Table 17), thus ensuring oxygenation of the pigment

The term "hemoglobin" is reserved here for the respiratory pigments of vertebrates only The hemoglobin molecule consists of the prosthetic (or active) group, heme, which is combined with a protein, globin Heme is the active or *prosthetic* group containing iron by means of which it can be combined with oxygen Although specific differences are shown in various animals, their hemoglobins are in many ways similar All hemoglobins evidently have the same heme, individual differences being due to the type of globin present, the number of heme groups, and the character of their linkage with other parts of the molecule The blood of different animals may be identified by the crystalline nature of its hemoglobin

If heme is set free from its linkage with the rest of the hemoglobin molecule, it is rather insoluble but combines readily with oxygen However, it does not dissociate readily Evidently globin performs a very important function in making the molecule more soluble and in some way aiding in the reversibility of its reaction with oxygen

The molecular weight of hemoglobin in human blood is approximately 67,000 and the pores in the walls of the blood capillaries of the kidney will allow substances of less than 70,000 molecular weight to pass through Therefore, if hemoglobin escapes from the corpuscle and dissolves in the plasma, it will be excreted by the kidney Claims have been made recently that hemoglobin is a threshold substance which may be present in the plasma in minute traces but which is eliminated by the kidney if it is present in high concentrations Much of the hemoglobin found in the plasma is destroyed by the liver

Erythrocruorin and *chlorocruorin* are structurally similar to hemoglobin both containing a heme group in their molecules These two pigments are present only in invertebrates and are at best less than half as efficient in carrying oxygen as mammalian hemoglobin Most generally they are dissolved in the plasma in which case their enormous molecules (mol wt = several million) prevent them from escaping through the capillaries

TABLE 17

The Respiratory Pigments of Animals and the Carrying Power of the Blood

Pigment	*Heme (or Hematin) Present*	*Active Metal Present*	*Color*		*Location in Blood*	*Where Found*	t_a *mm Hg*	t_L *mm Hg*	*Carrying Power (cc O_2 per 100 cc of blood)*
			Oxygenated	Deoxygenated					
Hemoglobin	Yes	Iron	Scarlet red	Deep red	Corpuscles	Vertebrates	27±	100	2.5–20
Erythrocruorin	Yes	Iron	Red	Red	Plasma	Annelids Mollusks	1–2	5–15	0.9–1.5
Chlorocruorin	Yes	Iron	Green	Green	Plasma	Annelids	9–30	26–50	9
Hemerythrin	No	Iron	Red	Colorless	Corpuscles	Annelids Polychaetes			2.7–7.2
Hemocyanin	No	Copper	Blue	Colorless	Plasma	Mollusks Crustaceans	4–15	15–35	0.74–5

Hemerythrin and *hemocyanin* contain no heme and in many other ways resemble each other Hemocyanin which is dissolved in the plasma may have a molecular weight over 10 million, hemerythrin, however, which is protected from loss by the corpuscle wall within which it is contained, has a much smaller molecule Thus, it is evident, that those pigments occurring inside corpuscles have much smaller molecules than those dissolved in plasma

Hemocyanin is a protein containing copper and molecules of the amino acids tyrosine, leucine, and serine and a sulfur compound as yet unidentified Evidently, oxygen is carried as it combines with copper

The heme molecule is very widely distributed in nature in the blood of animals from the lower forms in which a respiratory pigment is found to the highest mammal This is not so odd when one realizes that practically all living cells contain heme in the *cytochrome* molecule Cytochrome is important in oxidative metabolism of cells and is therefore, active in aerobic organisms Even in those animals having hemerythrin and hemocyanin in their blood stream, the body cells contain heme as an essential part of cytochrome

Many animals in their usual environment do not utilize the oxygen held by their respiratory pigments They evidently obtain sufficient supplies by direct diffusion into their tissues or from the oxygen dissolved in their plasma Their blood, therefore, remains fully oxygenated under ordinary conditions For example, the aquatic snail *Planorbis* contains erythrocruorin in its plasma—an exception, since most mollusks have hemocyanin The loading tension of this respiratory pigment is about 10 mm Hg partial pressure oxygen, the unloading tension, about 2 mm It lives in rather stationary or at most very slowly moving fresh water Under these conditions the blood is 100 per cent saturated with oxygen Since its unloading tension is very low, the erythrocruorin retains the oxygen and does not give it up to the tissues It is not necessary since the snail receives all the oxygen it needs by direct diffusion of oxygen from the environment into the plasma

However, there are periods, especially in small ponds, when heat from the sun's rays may drive off most of the oxygen from the water Consequently the oxygen diffusion into the plasma decreases and the tissues fail to get their proper supply Finally, when the oxygen tension in the tissues decreases below 10 mm Hg pressure, the organism draws upon the stored oxygen in the respiratory pigment Thus the animal is more apt to survive periods of stress The same type of system occurs in many marine forms, especially those living in the sand above the low tide mark Such

animals as the lugworm *Arenicola*, at the risk of asphyxiation, must dig down into the sand for protection, thereby endangering their lives They have however, an extra supply of oxygen stored in their respiratory pigments and as long as the low oxygen tension continues their blood can function in the same manner as vertebrate blood

MUSCLE HEMOGLOBIN

Muscle hemoglobin or *myoglobin* is found in some mammalian muscles imparting a red color to them it is not so concentrated in pale muscles Muscle hemoglobin has a different chemical structure and dissociates differently from blood hemoglobin its loading and unloading tensions are much lower than those of blood hemoglobins it is therefore similar to the respiratory pigments mentioned in the previous paragraph in its ability to remain in the oxygenated state This is true only when the muscle is at rest however as soon as it becomes active the oxygen tension is lowered rapidly and the myoglobin enters the picture as an instantaneously available store of oxygen It dissociates very rapidly below 10 to 15 mm oxygen tension (Figure 247) Its loading tension seems to be between 60 and 75 mm Hg This explains the fully oxygenated state of muscle when it is at rest

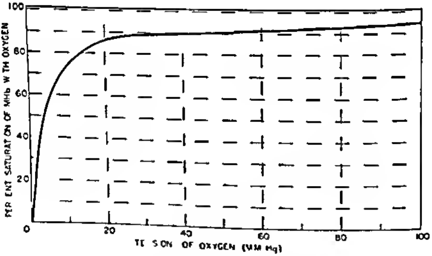


FIGURE 247

The dissociation curve for oxygenated muscle hemoglobin (MHb) There is no great increase in dissociation until the oxygen tension is decreased below 20 mm This indicates the function of MHb—the storage of oxygen for use in muscle

OTHER PIGMENTS

Two very interesting pigments about which very little is known have not yet been mentioned One of these occurs in the blood of a sea spider, *Anoplodactylus* giving a bright blue color to the blood Although it is contained within corpuscles there has been some suggestion that it might be a form of hemocyanin If so this would be the only known case of this pigment occurring in corpuscles

Another interesting substance is present in the blood corpuscles of tunicates These animals have a large number of colorless and a smaller number of colored corpuscles containing vanadium in various stages of oxidation that is in some corpuscles V_2O_3 is found in others V_2O_4 and still others V_2O_5 which gives to the corpuscles a green blue and orange color respectively The vanadium is linked with a larger molecule the whole being referred to as a chromogen it contains about 10 per cent vanadium Oxygen is taken up readily by the reduced form of the molecule it is given up freely, however only in highly acid solution It has been found that the corpuscles contain from 3 to 9 per cent free sulfuric acid There is still some question as to whether or not the vanadium containing compound functions in a respiratory fashion in physiological processes

CARBON MONOXIDE OR COAL GAS POISONING

Carbon monoxide as is generally known is a very effective respiratory poison It has been used to a considerable extent as a method of suicide and also has accounted for many accidental deaths

The respiratory pigments especially hemoglobin combine very readily with carbon monoxide, in the same way that they do with oxygen to form *carboxyhemoglobin* The affinity of hemoglobin for carbon monoxide is about three hundred times greater than that for oxygen Thus hemoglobin can be completely saturated with this gas present to the extent of only 0 5 per cent (it requires between 15 and 20 per cent oxygen for 97 per cent hemoglobin saturation) Carboxyhemoglobin dissociates at a rate one thousand times more slowly than oxyhemoglobin

Thus the danger of even extremely low concentrations of carbon monoxide in the environment is evident A person might show early symptoms of its effect when the air contains only 0.03 per cent carbon monoxide Vision and hearing become impaired and mental ability is lowered considerably when the blood is 40 to 50 per cent saturated with carbon monoxide; death occurs within a few minutes at only slightly higher saturation

When oxygen and carbon monoxide occur together, oxyhemoglobin can be formed only if the oxygen concentration is higher. For this reason, in treatment of carbon monoxide poisoning, the patient is given almost pure oxygen with sufficient carbon dioxide to stimulate heart and respiratory action.

CYANIDE POISONING

Cyanides have no effect on the oxygen carrying power of the blood. The mechanism involved in asphyxiation by this poison, therefore, is quite different from that of carbon monoxide. Most tissues and cells are dependent upon cytochrome and an enzyme, cytochrome oxidase, for proper oxidation, very little cellular oxidation in fact being possible without these substances. The cyanides are very effective in inhibiting the action of cytochrome oxidase and, thus, of cellular respiration. In cyanide poisoning therefore blood may be completely saturated with oxygen which the body cells cannot use.

Cyanide is poisonous because of the fact that it combines with iron in the oxidized (ferric) state. Thus, under normal conditions, hemoglobin does not react with cyanide since the iron remains in the ferrous state whether oxygen is being transported or has been released to the tissues. However, methemoglobin contains iron in the ferric state which will combine with cyanide. Therefore, in cyanide poisoning, substances capable of causing formation of methemoglobin (nitrites, thiosulfates, or methylene blue) may be of value since the cyanide would then be "bound" in the blood stream and not reach the tissues. Of course if too much methemoglobin were formed the blood would then not carry sufficient oxygen to the tissues, and a dangerous condition of a different type would result.

EXERCISE AND RESPIRATION

The oxygen consumed by the body at rest, is equal to about 0.25 liters per minute. Normally, there is no difficulty in breathing and the oxygen needs are readily satisfied. In exercise, the oxygen utilization increases in proportion to the work done and may reach 30 liters per minute. If the muscles do not receive sufficient quantities of oxygen, they go into oxygen debt (page 90) which means simply that lactic acid will collect in the muscles to be oxidized at another time. Sooner or later the oxygen debt (or lactic acid accumulation) will reach the point where fatigue sets in.

There is very little oxygen stored in the body, at best, about a 5 minute supply during rest. Actually, this is not a storehouse for oxygen but simply the amount of oxygen that happens to be in the body at any particular

time About 0.4 liters are found in the lungs, 0.8 to 0.9 liters in the blood, and about 15 cc in the tissue fluid

Every minute during exercise about 2 to 3½ liters of oxygen can be carried to the tissues in the body of an untrained individual In a trained athlete, however, about 4 liters can be delivered per minute If oxygen is needed above this quantity, the muscles go into oxygen *debt which is* not relieved until the person rests Respiration continues during rest at a rapid rate, oxygen consumption remaining high until all the lactic acid is oxidized

A trained athlete can go into a much greater oxygen debt than a novice at most, this would be equal to 20 liters of oxygen

There are at least two limiting factors in the amount of oxygen that can be delivered to the tissues of a healthy individual one is exercise of such a severity that there is too great a demand for oxygen, and the other is the inability of the heart to pump a sufficient supply of additional blood to the tissues

Many factors however, unite to contribute to a greater oxygen supply to the tissues These are (1) a more rapid respiratory rate, (2) deeper respiration, (3) contraction of the spleen thereby increasing the oxygen carrying capacity of the blood, (4) greater oxygen uptake by the blood in the lungs because of the low oxygen content of the venous blood caused by the exercise, (5) an increase in the heart rate along with an increase in stroke volume, (6) a shift in the blood by vasomotor action from the less active tissues to those (muscles) called upon to act at the moment, (7) greater dissociation of the oxyhemoglobin in the exercised muscles because of the low oxygen tension in them at the time

CELLULAR OXIDATION

All of the previous discussion on respiration has been concerned only with the transport of oxygen from the lung to the body cells where it is used in the oxidation of food materials Although blood itself is a tissue and the cells found in it necessarily use some oxygen the quantity consumed by blood cells is insignificant compared with that used by other tissues of the body

Comparatively little is known concerning cellular metabolism but certainly great strides have been made within the past twenty years toward this end By means of results obtained by various biochemical and physiological methods, our knowledge of oxidative mechanisms within cells has been increased

Exactly what happens between the time that oxygen enters the cell and

carbon dioxide is eliminated? The gaseous exchanges are only the beginning and the end of the story respectively It is known that there are many enzymes and coenzymes as well as hydrogen and oxygen acceptors within living cells Acceptors are substances that can combine loosely with and release readily hydrogen or oxygen within cells during metabolic activity The mechanism concerned with oxidation is not a simple one but appears as a long chain of chemical reactions which result in the liberation of carbon dioxide and water

OXIDATIVE ENZYMES

Enzymes in general are soluble colloidal organic catalysts produced by living protoplasm and usually destroyed by heat (above 45 to 50 degrees C) This definition applies to the oxidative enzymes within cells as well as to those taken up later in studies on digestion (Chapter 35) The latter are concerned chiefly with hydrolytic processes whereas the former aid in oxidative processes

Some of the coenzymes concerned in oxidative metabolism contain as prosthetic or active groups certain vitamins such as riboflavin niacin and thiamin Thiamin unites with other molecules to form within cells a coenzyme called *cocarboxylase* which acts with carboxylase in splitting off carbon dioxide from the carboxyl group of carbohydrates *Flavoproteins* are coenzymes or hydrogen acceptors of considerable importance in oxidation and are made up of a molecule of riboflavin (vitamin B_2) a protein and phosphoric acid Two coenzymes present in cells (coenzyme I and coenzyme II) are chemically diphosphopyridine nucleotide and triphosphopyridine nucleotide respectively and contain *nicotinamide* (niacin amide) as an active group Other substances such as vitamin C and glutathione evidently play a very important role in oxidation reduction reactions but our knowledge concerning their activity is very meager The student should understand that by oxidation is meant one of three types of reactions

1 Oxygen may actually be involved such as the oxidation of lactic acid to carbon dioxide and water

$$\underset{\text{Lactic acid}}{C_3H_6O_3} + 3\,O_2 \longrightarrow 3\,CO_2 + 3\,H_2O$$

2 A reaction may not involve oxygen at all but may simply consist of a loss of hydrogen as for example in the oxidation of reduced glutathione in the cell Glutathione is a compound built up by the union of three

amino acids—glutamic acid, glycine, and cysteine, this last containing an (—SH) group which is the active part of the molecule Thus we can represent its oxidation as follows

$$\underset{\text{Reduced glutathione}}{2\,G{-}SH} + O_2 \longrightarrow \underset{\text{Oxidized glutathione}}{G{-}S{-}S{-}G} + H_2O_2 \xrightarrow{\text{catalase}} H_2O + \tfrac{1}{2}O_2$$

3 There may be simply a loss of an electron to produce an oxidation, as is the case when iron changes from the ferrous (reduced) to the ferric (oxidized) state The loss of an electron causes the ions to become more positive

$$\underset{\text{Ferrous state}}{Fe^{++}} \longrightarrow \underset{\text{Ferric state}}{Fe^{+++}} + \underset{\text{Electron}}{e^{-}}$$

Always, whenever an oxidation process occurs, a reduction also takes place

SEQUENCE OF EVENTS IN CELLULAR OXIDATION

In general, we can group the processes occurring during oxidation into three classes according to whether the enzymes or other substances (1) activate hydrogen, (2) accept and carry hydrogen or (3) activate oxygen In most reactions the end product would be hydrogen peroxide but this is rapidly destroyed by the action of *catalase* another enzyme

There are three main groups of substances that are concerned with oxidative processes (1) The enzymes that act upon the food material (metabolite) to release hydrogen in an active form—*dehydrogenases* (2) The substances that accept the hydrogen and pass it on progressively from dehydrogenase to cytochrome—*coenzymes, flavoprotein* and *cytochrome* (3) The enzymes that activate oxygen from molecular oxygen—*oxidases* One such substance, called *cytochrome oxidase* found in cells is concerned with the presentation of active oxygen to active hydrogen held by cytochrome

There may be several mechanisms involved in cellular oxidation In fact, we know that one mechanism may be more active in some species than another For example, in many mammalian tissues, the cytochrome-cytochrome oxidase mechanism is almost 100 per cent active Therefore, if cyanide is added to such tissues it destroys cytochrome oxidase with the result that oxidation is brought to such a low level that living processes are impossible Two possible mechanisms may be presented as follows

MAINTENANCE OF NEUTRALITY AND CARBON DIOXIDE TRANSPORT IN THE BLOOD

Carbon dioxide is liberated continuously from the tissue cells into the blood stream, since the carbon dioxide of the blood flowing into the capillaries is low compared with that in the tissues This gas tends to produce an acid reaction in the plasma because it forms carbonic acid

$$CO_2 + H_2O \longrightarrow H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

Thus, if carbon dioxide is not removed the blood and tissue fluid would become quite acid About 5 per cent of the carbon dioxide is dissolved in the plasma, the remaining 95 per cent being changed into such forms as carbonic acid (H_2CO_3), bicarbonate ions (HCO_3^-) and carbamino hemoglobin The first two forms occur in the plasma the last, in the erythrocyte About 10 per cent of the total carbon dioxide is carried as the carbamino compound

Such substances as the carbonates and bicarbonates of the blood act as *buffers* and tend to hold the *p*H value constant Hemoglobin also acts as a buffer, as do the plasma proteins and phosphate salts The proteins owe their buffer action to the presence of amino groups ($-NH$) which can unite with acids, and carboxyl groups ($-COOH$) which unite with alkalis Because of their double action the amino acids are called *amphoteric substances* All of these substances act to maintain the neutrality of the blood and tissue fluid Thus in spite of the large quantities of carbon dioxide thrown into the blood stream, there is very little change in the acidity of the blood

THE CHLORIDE SHIFT

The red blood cells contribute to the efficiency of carbon dioxide transport by means of a phenomenon known as the chloride shift With samples of blood plasma one can demonstrate by means of a simple experiment the importance of the erythrocytes in this connection When carbon dioxide is bubbled through a sample of whole blood and an equal volume of plasma, it is found that the concentration of bicarbonate ions increases much more rapidly in the whole blood sample This is owing to the fact that the red blood cells present in whole blood contain an enzyme carbonic anhydrase, which greatly accelerates the formation of carbonic acid from water and carbon dioxide

However, this reaction like other chemical reactions would become slow and stop if the resulting products were to accumulate in too great a concentration To prevent this, the bicarbonate ions pass from the cells, where

they have been formed, into the plasma This would result in an ionic imbalance because of an excess of negative ion concentration (bicarbonate) if it were not for the *chloride shift* which occurs at the same time The chloride shift involves the passage of chloride ions from the plasma into the red blood cells, thus maintaining the ionic balance

In the lungs the condition is reversed Because of the relatively low concentration of carbon dioxide in the lungs, that material starts to leave the plasma Carbonic anhydrase now breaks down carbonic acid within the cell to carbon dioxide and water, the carbon dioxide enters the plasma and passes into the lung alveoli To keep this reaction proceeding properly, bicarbonate ions enter the erythrocyte from the plasma and, by carbonic anhydrase action, more carbonic acid is formed and broken down, the hydrogen ions are derived from reduced hemoglobin as the latter material combines with oxygen from the alveoli Owing to the greater increase of negative bicarbonate ions in the erythrocyte, the chloride ion passes from the cell to the plasma to maintain the ionic balance (Figure 248)

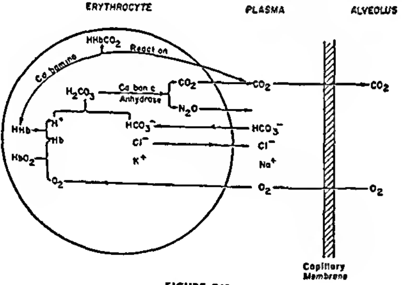


FIGURE 248

The chloride shift

As pointed out before, hemoglobin, functioning as carbamino-hemoglobin, also is efficient in carrying carbon dioxide, releasing it to the lung as illustrated The carbon dioxide combines directly with hemoglobin

$$HbNH_2 + CO_2 \longrightarrow \underset{\text{Carbamino hemoglobin}}{HbNHCOOH}$$

This combination accounts for 10 per cent of the total carbon dioxide content of the blood

From the foregoing it can now be seen how the pH of the blood is dependent upon the presence of buffer substances in it There are buffers that tend to prevent an increase in acidity and those that tend to prevent an increase in alkalinity The ratio between the two types is spoken of as the *acid base balance* Since the chief concern in the blood is the neutralization of acid (carbonic), most of the buffers are weakly alkaline in action and are altogether spoken of as the *alkali reserve*

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31

The Heat Regulatory System

TEMPERATURES OF ANIMALS

ANIMALS can be classified according to their body temperatures, as (1) *poikilotherms* (commonly referred to as cold blooded animals) which include all the invertebrate animals and most of the vertebrates, and (2) *homoiotherms* (commonly called warm blooded) which include only two classes of vertebrates the birds and mammals The term 'cold blooded is an erroneous one, the animals included under it are cold blooded compared to birds and mammals only if the temperature of the environment is colder than the body temperatures of the homoiotherms In summer, when environmental temperatures reach 100 to 110 degrees F, the blood of so-called cold blooded' animals is actually warmer than that of birds or mammals Thus the term *poikilothermic,* which means changing or varied temperature describes the conditions as found in animals whose blood is usually, but by no means always, cooler than that of mammals Homoiothermic means steady or constant temperature and more readily describes those animals, birds and mammals whose bloods are usually warmer than the external environment

POIKILOTHERMIC ANIMALS

The animals that belong to the poikilothermic group are well known to everyone They do not have a mechanism for regulating temperature but tend to take on the temperatures of the surrounding environment It

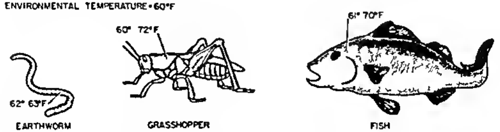


FIGURE 249

A comparison of body temperatures of three different poikilothermic animals (commonly referred to as cold blooded animals) when exposed to an external temperature of 60° F

should be noted that the animal temperature is usually slightly higher than the environment, a condition to be expected, since, if the animal is living, it is naturally metabolising and consequently producing heat which adds to its body temperature

HOMOIOTHERMIC ANIMALS

Many factors are involved in the more or less constant temperature found in birds and mammals, of the homoiothermic group In the first place, heat is produced within the body of the animal by oxidative processes accompanying general metabolic activity The essential basal metabolism alone produces sufficient heat for a homoiothermic condition but often this is supplemented by heat produced during muscular activity Thus at ordinary room temperature, 21 degrees C (or 70 degrees F), heat must be thrown off since a greater quantity is produced than the body needs for constant temperature

Actually, the temperature of these animals shows a great deal of variation The development of such a mechanism of temperature control has been gradual For example, some of the lower mammals supposedly having developed from reptilian forms, have much greater difficulty in regulating temperature than the higher mammals In some higher forms, such as the dog, rabbit, and cat, the heat control mechanism does not function at birth with the result that the young of these animals may be regarded as poikilothermic, although not so much so as the truly poikilothermic forms

The maintenance of a homoiothermic condition is partly regulated by means of nerve centers in the brain (the thalamic region) The cells in this region are very sensitive to slight temperature changes in the blood, and react accordingly, or they may be activated reflexly via impulses from the skin areas Sometimes this nervous mechanism may be disturbed in its normal action through the use of anesthetics or by lesions within the region itself The animal may, therefore, approach a poikilothermic condition and its temperature will tend to become the same as that of the environment

The constant, relatively high temperature of the mammalian body ensures a greater mental alertness along with physical activity

The processes that go on in the mammalian body, do so at various optimal temperatures In other words, some reactions are most rapid at 35 degrees C others at 40 degrees C, and still others at 50 degrees C Therefore, a change in body temperature would accelerate some processes while retarding others

BODY TEMPERATURE IN MAN

The normal temperatures for man range between 98 degrees F and 99 degrees F for oral or 99 degrees F and 100 degrees F for rectal (it is slightly higher for infants and young children—0 5 degrees to 1 degree F) He maintains this temperature over a wide range of environmental changes from below 0 degrees to above 100 degrees F Temperature changes occur quite frequently the range usually being much greater in infants, since their regulatory mechanisms are not yet perfected

The body temperature in man varies from early morning to late evening Usually the lowest temperature is found between the hours of 5 and 7 A M when it is slightly lower or greater than 98 degrees F (36 degrees C), the high point is usually reached between 4 and 7 P M after a gradual increase during the day the greatest temperature being about 99 degrees F (37 3 degrees C)

If a person should change his daily routine so that his working period would come at night and his sleeping hours during the day the low and high temperatures would soon reverse themselves

A great difference in temperatures occurs at different locations on or in the body Naturally, because of its direct contact with the external environment the temperatures of the skin are lower than those of the rest of the body at ordinary room temperatures

At room temperature (21 degrees C or 70 degrees F) that of the skin of the forehead may be around 90 to 92 degrees F but varying with the temperature and humidity of the surrounding air Inside the body, the heart temperature is found to be around 101 8 degrees F (38 8 degrees C) and that of the liver 104 degrees F (40 degrees C)

BALANCE BETWEEN HEAT PRODUCTION AND HEAT LOSS

Since heat is constantly produced in the body and since it is just as constantly lost from the body, there must be some means of maintaining a balance between the two processes In other words, heat production must equal heat loss in order that a constant temperature be maintained if the

production is greater than the loss, the body temperature rises, if it is less the body temperature falls

Heat is produced in the body chiefly by oxidation If the activity of an animal is increased the heat production increases correspondingly, and some mechanism must function to aid in driving off the extra heat On the other hand if the temperature of the environment decreases to a low level great quantities of heat are lost if certain mechanisms are not brought into play to overcome the loss The feathers of birds and the hair of mammals make excellent insulation This is especially true if a greater dead air space is formed at the base of the hair or feathers by their erection owing to the pull of the pilomotor muscles at that point (page 172) Man protects himself from too great a heat loss in cold environment by clothing himself appropriately

MECHANISM OF HEAT LOSS

There are several avenues for heat escape from the body by way of (1) excretory material (2) the lungs and (3) the skin

The heat loss by way of excretion is very small being about 2 per cent of the total loss This for the average individual is equal to about 60 calories per day Approximately 14 per cent of the heat is lost through the lungs or about 420 calories and 84 per cent by way of the skin (2520 calories) Altogether about 3000 calories are lost every 24 hours

Heat Loss by Way of Lungs and Excretion

Sweat is a form of excretion but it will be considered with heat loss through the skin The urine and feces are included here, although the heat loss is rather small compared to the other outlets

A much greater amount of heat is lost through the lungs than by excretions The inspired air is heated when it enters the lung about 4 per cent of the total heat being lost in this manner In addition heat is lost as the result of evaporation since the air in the lungs becomes saturated at body temperature Animals such as the dog and cat do not sweat as do humans their sweat glands being situated on the pads of their feet Loss of heat through the lungs by way of water vapor is therefore a very important outlet In hot weather dogs increase their water elimination by panting

of air that collide with it, (3) *conduction*, which is the transmission of heat energy by molecular vibration, that is, heat transmission from a warm body to a cold one by the transfer of molecular movement within the warm body, to the cold one, (4) *evaporation* of sweat.

The degree of dilatation of the blood vessels of the skin determines the amount of heat brought to the surface, thus determining the temperature of the radiating surface.

The heat loss is much greater by way of these processes on a cold day than on a warm or hot day when the skin may actually absorb heat from the air, although other factors continue to aid in heat loss. Heat prostration increases during summer months when both temperature and humidity are high. Humidity prevents sweat from evaporating and the body temperature thus tends to increase.

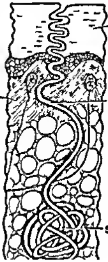
REGULATION OF BODY TEMPERATURE

It is known from experience that a spinal mammal is unable to regulate its temperature. Such an animal must be kept warm artificially if it is to survive at all. The same is true for a decerebrate and a midbrain animal. These animals never sweat or shiver when exposed to heat or cold, respectively. It has been found that if the hypothalamic region, just above the red nucleus, is intact the animal can maintain a constant temperature. This is called the *temperature* or *heat center*.

If an intact animal is exposed to cold, several reactions occur in order to prevent too great a heat loss. These may be reflex in action by way of sensory nerves to the hypothalamus, or they may be caused by the slightly cooler blood which when it reaches the hypothalamus, stimulates neurons leading to striated muscles, pilomotor muscles, adrenal glands, and vasomotor and cardiac centers in the medulla. The respective responses are as follows: (1) There is an increase in the tone of the striated muscle which finally leads to shivering. This act produces more heat. (2) Other motor discharges pass to the medulla of the adrenal gland causing greater flow of adrenalin which increases the rate of oxidative metabolism and consequently results in increased heat production. (3) Impulses to the vasomotor centers bring about a constriction of the peripheral blood vessels thus routing the blood through deeper parts of the body, and in this way prevents too great a heat loss. The heart rate is also increased and aids in the distribution of heat. If the cooling is local, only that area is affected. (4) The pilomotor mechanism becomes active, causing the hairs to rise. In man, this reflex, which results merely in the formation of "goose flesh," has lost its value but

in the birds and furry mammals it gives greater protection against heat loss Man must resort to clothing

If an animal is exposed to heat, impulses affect a region in the hypothalamus and the following reactions are observed (1) Impulses pass down the cord and over sympathetic neurons to the sweat glands and cause them to secrete, thus increasing the heat loss (2) By way of the medulla, vasodilator nerves carry impulses to the blood vessels and increase the blood supply to the skin region It is also true in this case, that if the heating is local, the effect is local



FEVER

When the temperature of the body is greater than normal, the condition is called fever Many diseases are accompanied by an increase in temperature Temperature charts are made for severe cases, especially those which are hospitalized An expert can to a certain extent diagnose type of disease by such a chart

whether or not we should attempt to overcome the condition unless the life of the person concerned is in immediate danger. Temperatures up to 105 degrees F. may be beneficial to the body in their effect upon the organisms or mechanism producing the increased temperature, but above 105 degrees F., it becomes dangerous. The limit for humans is about 108 degrees F.

SUNSTROKE AND HEATSTROKE

Sunstroke is caused by excessive exposure of the head to the heat of the sun's rays. It increases the temperature of the brain which causes the cerebral arteries to dilate and the cerebral blood pressure increases. This may bring about paralysis of some of the vital centers in the cerebrum and medulla, especially those controlling respiration, heart action, and vasomotor action. A hat acts as a protection to a certain extent since the air space between it and the head is good insulation. If the air immediately in contact with the skin of the head is continuously replaced, as by a person moving about freely, the conditions that lead to sunstroke are minimized.

Heatstroke is an excessive accumulation of heat within the body occurring if one is too heavily clothed or if one exercises too strenuously without resting or cooling off. It is a common occurrence in tropical regions and may be fatal. Body temperatures may rise to 41 degrees C. (106 degrees F.) or even 43 degrees C. (109 degrees F.), at which level conditions are almost hopeless.

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Part Seven

NUTRITION and ELIMINATION

32

The Food of Animals

NEED FOR FOOD

THE FOOD MATERIALS needed by living organisms have three main functions (1) production of energy, (2) provision of materials for incorporation into the protoplasm of cells, and (3) contribution to the general well being and proper metabolism for maintenance of life processes The two last mentioned functions are undoubtedly closely related Materials may be used to replace old worn out protoplasm or to synthesize new protoplasm (growth) Although we recognize the need for substances such as proteins, fats and carbohydrates to ensure growth and function, we must realize also that the animal body could not survive for long without vitamins and minerals, as well as water Even carbon dioxide, which we have come to regard as a waste substance of the metabolic processes within cells, has been shown to be beneficial in the proper growth of certain protozoan forms

Growth occurs in both nonliving and living matter In nonliving matter it is usually spoken of as *growth by accretion* Sodium chloride crystals, for example, grow in this way, but only if the surrounding solution is saturated with sodium chloride The molecules of sodium chloride solution simply add to those already present in the crystals Growth in living matter, or protoplasmic growth, is *growth by intussusception*—a process in which the substance already existing (protoplasm) endowed with the property of acquiring and utilizing simple materials, builds them into its own complex substance, that is, protoplasm

The animal, therefore, must first obtain food prepare it for absorption by digestive processes, if necessary, and then pass it on to the body cells for use

ESSENTIAL ELEMENTS

Protoplasm contains and needs a great number of different elements, especially those of lower molecular weight It is often difficult to say whether all of the elements present are essential to the life of the organism, or whether some are present merely because of mechanical absorption from the environment It is known, however, that many more elements are essential than were once believed to be indispensable

About 95 per cent of living matter consists of four elements—oxygen carbon hydrogen and nitrogen small amounts of such elements as sodium potassium calcium magnesium iron phosphorus and sulfur are present also as well as minute amounts of many others

Naturally these elements must be taken in with the food material Sometimes animal systems are very efficient at concentrating within their bodies trace substances of the environment It will be recalled that in Chapter 30 brief mention was made concerning the presence of vanadium in the blood stream of the marine animals the tunicates Vanadium has never been detected in sea water by known chemical methods yet these animals can extract relatively large quantities from the water in which they live A similar case is that of marine mollusks which extract copper for use as part of the hemocyanin molecule in their blood stream although this element is in extremely low concentration in sea water—about one part in one billion

THE TYPES OF FOOD USED BY PLANTS AND ANIMALS

Since animals cannot utilize most elements as such their nutrients usually consist of very complex chemical compounds such as protein fats carbohydrates vitamins and the less complex inorganic salts and water Most of the colorless plants are also dependent upon complex materials as foods Even the protozoans generally require the same types of food that higher animals require The simplicity of organ and organism structure is no criterion of protoplasmic condition which is as complex in the simplest organism as in the highest The complexity of higher organisms is a result of the formation of specialized tissues and organs from great numbers of cells

CHEMOSYNTHESIS AND PHOTOSYNTHESIS

Some bacterial forms are capable of synthesizing complex organic materials from carbon dioxide and water by the process of *chemosynthesis* This means simply that the energy required for the synthesis is obtained by oxidation of substances in the reduced form such as ammonium chloride and hydrogen sulfide *Nitrosomonas* a bacterial genus by means of the energy liberated when ammonia is oxidized to nitrite produces new protoplasm

Most plants have a green pigment, chlorophyll which usually has a prominent location in the plant in so far as exposure to sunlight is concerned *Photosynthesis* is the process in which carbon dioxide and water are united in the presence of light, with chlorophyll as a catalytic agent to form carbohydrates In other words through the action of chlorophyll the radiant energy of sunlight is changed into chemical energy by the union of carbon

dioxide and water to form starch. It is not known whether this process or chemosynthesis was the first to appear in living matter; more than likely, chemosynthesis existed long before the development of chlorophyll.

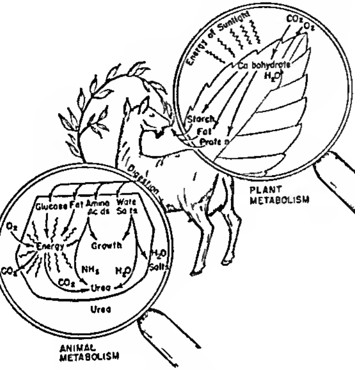


FIGURE 251

Animal and plant metabolism contrasted. (Redrawn from Pauli: *The World of Life*, by permission of Houghton Mifflin Co.)

Some investigators maintain that the earth was at one time a molten mass which gradually cooled, completely enveloped at first by enormous clouds of steam, so that no sunlight could penetrate.

Protoplasm, capable of chemosynthesis, could have originated in this darkness, and chlorophyll may have developed later, when the clouds disappeared and the sun's rays reached the earth.

Some animals, such as termites, goats, cows, and horses, can utilize cellulose and the hemicellulose making up the woody parts of plants. The actual digestion, however, is carried out in the alimentary tracts of these animals by enzymes produced by microorganisms living there symbiotically. The termites do not need protein or amino acids in their diet, although nitrogenous substances are absorbed through their alimentary tracts and used in protein synthesis within their bodies. It is believed that microorganisms in the intestine may utilize atmospheric nitrogen in the production of complex nitrogenous substances needed for body repair and growth.

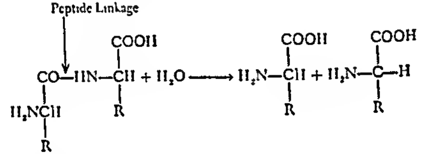
PROTEINS

The proteins are the most important and also the most complex constituents of protoplasm, having very large molecules, as indicated by their molecular weights. Hemoglobin, a protein, has a molecular weight around 67,000, and some of the hemocyanins, above 10 million.

Proteins are indispensable for life and, therefore, occur in all living substance. The elements carbon, hydrogen, oxygen, and nitrogen are always found in proteins; sometimes phosphorus, sulfur, and iron also are present.

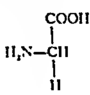
The nitrogen and carboxyl content of protein is significant since it is through the amino ($-NH_2$) and carboxyl ($-COOH$) groups that protein linkages are made possible.

Upon analysis, it is found that proteins consist of amino acids. These are formed when a protein is broken down by hydrolysis, a process by means of which water is added to the various parts of a molecule so that the molecule is stabilized as soon as it is separated. For example,

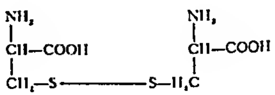


The union between the amino and carboxyl group is called a *peptide linkage*. If two amino acid molecules are joined in this manner they form a dipeptide; if three, a tripeptide; and if there are many amino acids, they form a *polypeptide*.

The human body contains twenty-one to twenty-five amino acids, all of which can be combined in different ways to produce different proteins. The student can obtain a list of them and their formulae from any textbook in biochemistry. The simplest amino acid is glycine; cystine is one containing sulfur:



Glycine



Cystine

Other amino acids are much more complex than these and may have *aromatic*, *indole*, and *pyrole* nuclei. Because of the presence of these groupings, it is possible to make qualitative color tests for proteins. Precipitation tests also are useful and are initiated by (1) concentrated acids, (2) salts of heavy metals, and (3) reagents such as tannic, picric, and chromic acids. Proteins are coagulated by heat, the change altering their nature.

Specific individuality in living systems is possible because of the enormous numbers of different proteins that can be produced simply by a change in an amino acid or in its linkage within the protein molecule. Even the proteins of the bloods of humans differ so that the blood of one person may not be compatible with that of another.

When taken into the bodies of animals as food, the proteins cannot pass through the membrane of the intestinal wall. Therefore, they first must be broken down into amino acids. It is possible that an animal can exist without protein in its diet, if given the proper mixture and proportion of amino acids with other essential foods. The animal cell can synthesize some amino acids but usually only the simpler ones. It evidently cannot synthesize the more complex groupings, those which contain the ring groups must be supplied by preformed proteins. The following amino acids are said to be indispensable to higher animals: lysine, valine, tryptophane, methionine, histidine, phenylalanine, leucine, isoleucine, threonine, and arginine. Some proteins are inadequate because they do not contain all of these essential amino acids. Thus the protein in corn is deficient in amino acids needed for growth. Many different protein foods should, consequently, be used in the diet.

CARBOHYDRATES

Carbohydrates are the chief source of energy in animals. They are assimilated by plants in the photosynthetic process. The plant can then use, in the production of proteins, its carbohydrates and the nitrogenous substances entering it from the soil by way of the root system.

Carbohydrates are made up of three elements—carbon, hydrogen, and oxygen. The hydrogen and oxygen are usually in the proportion necessary to form water. Glucose, $C_6H_{12}O_6$, has hydrogen and oxygen in proportion to form six molecules of water. Since there are exceptions to this rule, the carbohydrates have been defined as the *aldehyde* or *ketone derivatives of polyhydric alcohols*. Glucose, for example, has the formula as shown in Figure 252 which is an aldehyde derivative of a polyhydric alcohol, whereas fructose is a ketone derivative.

Glucose, fructose, and galactose are *hexose* sugars having six atoms of carbon in their molecule, empirically the same for all—$C_6H_{12}O_6$. Any sugar with this formula is called a *monosaccharide*. The carbohydrates must be hydrolyzed to monosaccharides in the alimentary tract of mammals before absorption can take place. Glucose is the most common of all and is the only carbohydrate utilized as a source of energy in the mammalian body. If other monosaccharides are present they may be absorbed, but are quickly transformed within the liver into glucose.

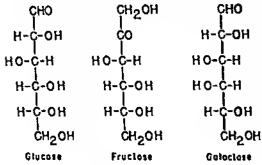


FIGURE 252

The monosaccharide sugars

The *disaccharides* all having the same empirical formula, $C_{12}H_{22}O_{11}$, are formed by the union of two monosaccharide molecules with the loss of one molecule of water. The disaccharides, sucrose, lactose and maltose, may be broken down by hydrolysis into simple sugars, this action being aided by enzymes found in the small intestine.

$$\text{Sucrose} + H_2O \longrightarrow \text{Glucose} + \text{Fructose}$$
$$\text{Lactose} + H_2O \longrightarrow \text{Glucose} + \text{Galactose}$$
$$\text{Maltose} + H_2O \longrightarrow \text{Glucose} + \text{Glucose}$$

Because of the presence of the aldehyde or ketone groups, the sugars are good *reducing agents*. They will take up oxygen from other substances and then become oxidized themselves, a characteristic utilized clinically in the determination of blood and urine sugars. If a solution, such as the blood or urine of a diabetic person, is boiled with a small quantity of copper sulfate, a yellow to reddish precipitate is formed. The cupric sulfate is reduced to cuprous oxide due to the action of the aldehyde group of the glucose molecule. This reaction is obtained with all three of the monosaccharides as well as lactose and maltose, but not with sucrose. The sucrose molecule is formed by the union of the ketone group of the fructose molecule with the aldehyde group of the glucose. Hence they are not free to exert their reducing action.

Evidently the body can form carbohydrates from fats and proteins. Thus, it is difficult to produce evidence in respect to the necessity for carbohydrate in the diet. However, the evidence at hand seems to indicate that the animal must have carbohydrates in its diet if it is to remain in good physical condition.

Glucose is stored in the animal body (chiefly in the liver and skeletal muscles) in the form of *glycogen* (animal starch), and in plants as plant starch and the celluloses of plant walls, such materials are called *polysaccharides.* The molecule of starch consists of twenty four to thirty molecules of simple sugar, whereas that of glycogen has about twelve or fifteen molecules, cellulose has many more

FATS AND LIPOIDS

Fats and lipoids are important constituents of most foods and, evidently, in mammals some of the energy during normal activity is obtained from this source. Cholesterol and phospholipids, such as lecithin, are of great importance to the normal functioning of the cell, making up the cell membrane and functioning in permeability Fats can be produced from carbohydrates, as is witnessed by the excessive accumulation that occurs in some individuals who eat large quantities of the latter, such as candies and other sweets.

The neutral fats or true fats are defined as the *triglycerides of fatty acids* This refers to the union of one glycerol molecule with three fatty acid molecules to form a fat The type of fat depends upon the fatty acid molecules Glycerol is an alcohol and, like all other alcohols, contains the —OH group connected to its carbon atoms, since it has three carbon atoms, it, therefore, has 3 —OH groups A fat is produced if three molecules of fatty acid, such as stearic acid, unite at the position of the —OH groups of the glycerol.

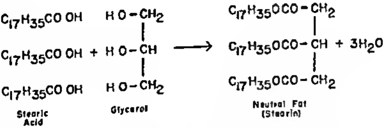


FIGURE 253

Production of fat by union of glycerol and stearic acid

The fats are insoluble in water but are soluble in alcohol, chloroform, ether, and benzene They are crystallizable although their waxlike texture would suggest otherwise They are probably present in all living material, plant and animal The importance of lipoids (fatlike materials) is much more evident than the importance of fats although certain fatty acids, such as oleic, seem to be essential to proper functioning and formation of the

skin, a deficiency in these may lead to skin rashes, curable by the addition of the fatty acids to the diet Such lipoids as cerebrosides and phospholipins probably occur in every living cell, in nervous tissue these seem to be especially abundant although they are plentiful also in other tissues Cholesterol is found in cell membranes, sometimes that in the bile crystallizes out in the gall bladder and forms gallstones which may interfere with the flow of the bile

INORGANIC SALTS AND WATER

The importance of inorganic salts and water has already been emphasized Many elements in the form of inorganic salts are essential The salts of sodium potassium, calcium, magnesium, iron, copper, and phosphorus are of especial interest and have been studied to a greater extent than the salts of other elements The first forms of these elements have been studied by many investigators in reference to ion antagonism and other phenomena They are chiefly the concern of the cellular physiologist but it is interesting to note that usually an antagonism exists between the action of the monovalent and bivalent ions For example, sodium and potassium tend to solate protoplasm while calcium has the opposite effect Both types must be present in order to strike a proper balance The same antagonisms are shown in the action of these ions on the heart

ADDITIONAL READING

Albanese A A *Proteins and Amino Acid Requirements of Mammals* (New York Academic Press, 1950) A detailed clinical account

Sherman H C, and C S Lanford *Essentials of Nutrition*, 2nd ed (Macmillan, 1943) General considerations of food and diet

Soskin S, and R Levine *Carbohydrate Metabolism* (University of Chicago Press 1952) General discussions of carbohydrate utilization in the body and influencing factors

33

The Vitamins

VITAMINS are accessory food substances, required by the body in rather minute quantities. They are difficult to define specifically but in general they may be said to consist of *organic substances essential to proper functioning of the body as a whole*. From the very beginning of research on vitamins, scientists suspected their relationship to enzymes since only extremely small quantities of the substances are necessary to produce a specific action. Recent work has substantiated this supposition.

It is difficult to designate any particular person as the discoverer of the vitamins. The vitamin C deficiency disease, scurvy, was known to the ancient Greeks and especially to mariners during long voyages. These deficiency diseases were usually suspected of having been produced by some injurious substance in the diet. In 1772 Captain Cook, an English explorer, made an extended three year voyage, noted in history because of the fact that his crew did not develop scurvy. He claimed this to be the result of use of fresh fruits and vegetables. Whenever the ships stopped at a port, they were loaded with all of the fresh foods they could secure. As a consequence, his men remained in good health.

Beriberi was well known to the ancients and it also, was believed to appear because of some injurious substance in the diet. It has occurred especially in Asiatic races among the Chinese, Japanese, and Indians, who use polished rice as their staple food. In the years immediately preceding the recognition of beriberi as a deficiency disease, it was thought to be caused by a fungus on rice. However, in 1887 the Japanese found that an increase in the variety of food served to check its appearance. The disease did not occur among their soldiers and sailors during the Russo Japanese War in 1904, the same foods that formerly had seemed conducive to the disease were used with rice as a staple but in addition, the men received fresh fruits and vegetables. Thus, it was realized that the disease could not be caused by the presence of a toxic substance in the diet or by a disease producing organism.

In 1897, a Dutchman by the name of Eijkman came very close to a solution of the problem. Birds are very susceptible to certain vitamin deficiencies and develop *polyneuritis*, a condition similar to beriberi in hu

mans Eijkman discovered that chickens developed polyneuritis when fed polished rice, but could be cured if given the rice polishings He, however, failed to realize, as did others, that a dietary factor was involved, but suggested that some toxin present in the polished rice was active in producing the disease He thought that the polishings contained a substance inhibiting the action of this toxin

Actually the first studies made on vitamin action were histological (that is studies made on the effects of vitamins on tissues), although nothing was yet known about the physical or chemical characteristics of vitamins These investigations, carried out some fifty years ago, have been confirmed again and again Scientists found that the nerves of birds and mammals afflicted with polyneuritis or beriberi, show a degeneration of the myelin sheaths It is generally known now that the nervous system is especially affected by this deficiency

Until the early part of this century, the diet requirement of animals was thought to consist only of water, carbohydrates, fats and proteins plus small quantities of inorganic salts The English biochemist, F G Hopkins, in 1906, evidently recognized the necessity for additional substances, but he did not publish experimental proof for his theories until 1912 McCollum (1913) and his co workers in this country also recognized the necessity for accessory food substances' in the diet Funk, in 1911, had used the term *vitamine* to describe one of these factors, but McCollum discovered that the one he was working with contained no amino group Later, the e was dropped and we still use the term *vitamin* except where the chemical nature has been established

The vitamins may be grouped into those that are fat soluble (A, D, E, and K) and those that are water soluble (B complex and C) The use of the alphabet for identifying the vitamins is fast disappearing as their molecular structures become known and their chemical names can be applied accurately

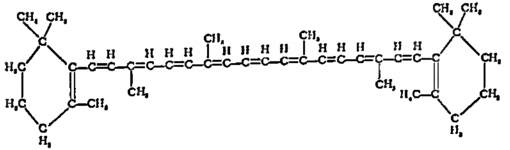
VITAMIN A (ANTIXEROPHTHALMIC VITAMIN)

McCollum discovered this vitamin, calling it "fat soluble A" As yet no common chemical name has been given to it, although the chemical formula is known Vitamin A is derived from plants in the form of carotene Some relationship exists between the green or yellow color of plants and the amount of carotenoid present The carotenoids are found generally throughout the plant kingdom, often associated with another closely related plant pigment, xanthophyll

Some of the common plant foods that may furnish us with a good supply

of carotenes are yellow sweet potatoes the outer green leaves of lettuce, carrots, yellow corn, spinach, string beans, green peas, cantaloupe, bananas, and pumpkin The so-called "white vegetables have very little The best animal sources of vitamin A are fish and mammalian liver, and such dairy products as butter, cream, and egg yolk Cod liver oil and halibut liver oil are especially rich in this vitamin, converted by the fish from carotene obtained from algae, diatoms and other marine plants Large fish may secure vitamin A directly by feeding upon smaller fish which have constructed it from carotene Since plants never form vitamin A, and animals are able to produce it only from the provitamin carotene, animals are, therefore, ultimately dependent upon plants for their supply

Of the several carotenes existing in nature, beta carotene having the following formula is of chief importance, since it furnishes two molecules of vitamin A



Beta Carotene

In the bodies of mammals, the carotenes are emulsified by the action of bile salts They are transformed into vitamin A as they are absorbed through the intestinal walls, and are then carried to the liver where they are stored The conversion of carotene is slow and incomplete, only about 20 per cent being changed to vitamin A How this occurs is not known, but it is thought to be initiated by an enzyme, carotenase Large quantities of vitamin A are stored in the liver of mammals and of certain fish, the liver of certain species of halibut containing almost 1 per cent by weight

The concentration of vitamin A in the liver of the newborn infant is low Evidently it is not transmitted through the placenta, but during the first few weeks after birth, the supply stored in the liver gradually increases, from that contained in the milk The vitamin A concentration is high in human milk, especially in the colostrum (the first fluid secreted by the breast following birth, page 569) and early milk

Vitamin A soluble in fats and fat solvents, has been isolated in crystalline

form It is readily oxidized in the presence of oxygen, but is quite resistant to heat in the absence of oxygen It may be absorbed in the absence of bile but the carotene must first be emulsified Therefore, in cases of bile deficiency, either the pure vitamin is fed or bile salts added to the diet, in order to ensure the absorption of the carotenes

Effects of Vitamin A Deficiency

Numerous symptoms result from vitamin A deficiency

1 *Retardation in growth* When the vitamin was first discovered, it was called the growth vitamin, but failure of an organism to grow in its absence is only one of its characteristics

2 *Nightblindness* One of the most outstanding changes found in vitamin A deficiency is a decrease in the ability of the eyes to become dark adapted, a condition called "*nightblindness*" or *nyctalopia* (page 244) This condition as well as its treatment, has been known for centuries but knowledge concerning the mechanism involved has been accumulated only recently

The *visual purple* or *rhodopsin* found in the peripheral segments of the rods of the retina contains vitamin A in its molecule The formation of visual purple in the eye depends upon the presence of vitamin A The breakdown of the visual purple, producing visual yellow when light strikes the retina, has been clearly described (Chapter 18)

$$\text{Visual purple} \underset{\text{dark}}{\overset{\text{light}}{\rightleftharpoons}} \text{Visual yellow (Retinene)}$$

The energy produced by this reversible reaction is utilized by the nerve endings in initiating the impulse The resynthesis is not 100 per cent efficient and, therefore, some of the vitamin, along with other parts of the rhodopsin molecule is lost It is obvious, therefore, that there must be a continuous supply of vitamin A available for use in the retina

3 *Xerophthalmia* An inflammatory condition of the eyes known as *xerophthalmia* also results from a deficiency of vitamin A, the function of the lacrimal glands seems to be suppressed, the cornea becomes dry and is thus exposed to infection The lacrimal fluid, lacking in this condition, is normally bactericidal and, hence, a protection against infection

4 *Keratinization of epithelium* A keratinization of epithelial tissues—a dryness and scaliness of the skin and cornification of the epithelial linings of the respiratory, alimentary, and urinary tracts—is present in vitamin A deficiency Many of the glands show a suppression of their secretions

Early workers suggested that a deficiency in vitamin A was responsible

FIGURE 254

Scaly skin rash (upper arm) caused by vitamin A deficiency (Reproduced by courtesy of Parke Davis and Co)

for a lowered resistance to various diseases Keratinization and dryness of tissues may lead to openings produced in the integument more readily but there is no proof of a decrease in resistance unless it is in the conjunctiva of the eye due to lack of the bactericidal tear fluid In other words probably a surface resistance is involved rather than an internal one

Requirements

Vitamin A is generally available from natural sources where its concentration is not exactly known Several tests or assays may be used in order to determine the vitamin content one of the most common being to compare the rate of growth of rats fed the natural source of vitamin A with that of rats fed a known quantity of crystalline beta carotene An international unit is equal to 0 0006 mg of this carotene

In adults with a properly mixed diet supplementary sources are unnecessary, but it is so essential a substance for growing children that it is wise to add a portion of it to their diets A daily requirement of about 6000 to 8000 units is recommended for children for adults the requirement is from 3000 to 5000 units per day

Vitamins A_1 and A_2

Apparently at least two forms of this vitamin exist, vitamin A_1 and A_2, both containing the same number of carbon atoms but in different molecular arrangement. The following diagram indicates the relationship between the different types of vertebrates and the type of vitamin A occurring in them.

Marine fishes (Vitamin A_1)

Catadromous fishes (Vitamin A_1, chiefly, but also A_2)

Anadromous fishes (Vitamin A_2, chiefly, but some A_1)

Land vertebrates (Vitamin A_1)

Amphibia (Vitamin A_2, chiefly, but also A_1)

Fresh-water vertebrates (Vitamin A_2)

Anadromous fishes, of which the salmon is an example, are those spending most of their lives in the sea, but returning to fresh water to spawn. *Catadromous* fishes, such as eels, are those living in fresh water but going into the sea to spawn.

Vitamin A_2 becomes part of the *porphyropsin* molecule (found in the retinas of some lower vertebrates) which is the counter part of rhodopsin. Although the reactions that occur with porphyropsin are not well known, it seems to undergo changes similar to those of rhodopsin upon exposure to light. In man, where visual sensation is dependent upon rhodopsin, vitamin A_2 is of very little value.

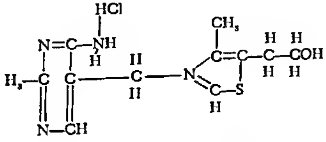
The Vitamin B Complex

The original vitamin B complex consisting of many vitamins, or factors, when first studied was referred to as the B, the antineuritic, or antiberiberi vitamin. The difficulty in early separation lay in the fact that most sources for the one are also good sources for the other, all types being soluble in water. However, not long after the B complex was discovered, it was separated into two parts, the one was called vitamin B for some years and the other vitamin G (or the growth and the antipellagra vitamin). Later, they were referred to as B_1 and the B_2 complex (consisting of many factors) respectively.

THIAMINE OR VITAMIN B_1 (ANTINEURITIC VITAMIN)

Thiamine, the antineuritic vitamin, has been isolated and synthesized. It is produced only in plants, is stored in very small amounts in animal tissues, is water soluble, and is fairly stable in acid solution.

Chemically it consists of two distinct parts, a thiazole and a pyrimidine nucleus, which are easily separated in neutral or alkaline media. The name, thiamine, is derived from the fact that its molecule contains sulfur and has the following structure:



Pyrimidine Thiazole

Thiamine hydrochloride

Because of its destruction at high temperatures thiamine is not present in canned foods. However, it is quite resistant to ordinary cooking.

Most fruits and vegetables are not good sources of this vitamin although they do add some to the diet. Whole grains, yeast, peas, and beans are well supplied with it, whereas lean meat, eggs, milk, and cheese contain small amounts. Some bacterial synthesis of thiamine may take place in the intestine but the quantities synthesized are not sufficient for meeting body requirements.

Deficiency of Thiamine

Beriberi, the disease caused by thiamine deficiency, exists in two forms, dry and wet, the former associated with nervous disorders, the latter with circulation. Dry beriberi, or polyneuritis develops if the thiamine content of the body becomes very low. Inflammation occurs in the peripheral nerves leading to a progressive paralysis of the limbs. Sensory mechanisms are also involved.

Polyneuritis is most readily induced in birds, the pigeon being especially susceptible to deficiency. If pigeons are placed on a polished rice diet for several weeks they soon show symptoms such as limb and wing paralysis

and retraction of the head These symptoms rapidly disappear if the bird is given small amounts of thiamine by mouth Sometimes an apparent recovery is made within twenty minutes to one hour after treatment depending upon the condition of the animal and upon the dosage

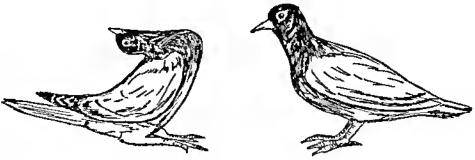


FIGURE 255

Pigeon showing the effects of deficient thiamine intake Left pigeon suffering from polyneuritis the equivalent of beriberi in man right same bird an hour after treatment with thiamine (Redrawn from *The Human Body and Its Functions* Revised Edition by C H Best and N B Taylor By permission of Henry Holt and Company Inc copyright 1948)

Wet beriberi manifests circulatory involvement with edema The signs and symptoms of cardiac failure may be lacking entirely in the early stages Sometimes the first sign is a sudden circulatory collapse the lungs being congested and the heart greatly dilated which may result in death

Thiamine deficiency is said to arrest growth which is true for several of the vitamins for apparent reasons

Loss of appetite and loss of tonus of the smooth muscles of the gastrointestinal tract are early symptoms of an inadequate thiamine supply The direct effect of thiamine deficiency however may be on the nerves leading to the digestive glands and smooth muscles which thus fail to function properly As a consequence a marked failure of the digestive processes may follow

Alcoholic Neuritis

Chronic alcoholism is a common cause of thiamine deficiency and indirectly of neuritis Alcohol which is vitamin free replaces food containing essential factors of nutrition in the diet of the habitual drinker One quart of whiskey provides 2800 calories the total daily requirement of an adult male Alcohol as such is not the cause of the progressive neuritis which may lead to alcohol psychoses but rather it satisfies the caloric need of the body without furnishing the essential vitamins It has been shown

that symptoms of the thiamine deficiency disappear if adequate amounts of thiamine are supplied, even though the alcoholic intake is continued

Requirements

Most animals require thiamine in their diet There is still much to learn concerning the requirements of invertebrates but even those that seem to get along nicely without it, may still need it, they may synthesize it themselves or have it synthesized within their alimentary tract by symbiotic organisms (organisms that live within a host body, with the host and the organism benefiting by the association)

The quantity of this vitamin required for humans varies with the individual as well as with the amount of work he does Heavy work adds to the carbohydrate breakdown which in turn requires adequate supplies of thiamine It has been suggested that 1 2 mg to 2 5 mg daily should be taken with the diet containing from 2500 to 4000 calories respectively Much more than this is needed during pregnancy

Fundamental Action of Thiamine

We naturally look for this fundamental action of thiamine in the cells and tissues themselves It has been shown that in brain tissue of polyneuritic animals there is an accumulation of lactic and pyruvic acids but the addition of thiamine to the diets of animals results in an increase in oxygen uptake as well as in the removal of the acids This same action has been found to occur in other tissues—the kidney heart, and liver Thus, vitamin B is not only active in nervous tissue, but in others as well

The final step in the breakdown of glucose is the transformation of pyruvic acid to acetaldehyde and carbon dioxide Lactic acid, produced during metabolism, is converted to pyruvic acid

$$\underset{\text{Lactic acid}}{CH_3CHOH\ COOH} \longrightarrow \underset{\text{Pyruvic acid}}{CH_3CO\ COOH} + 2H$$

By the action of an enzyme, *carboxylase*, the pyruvic acid is converted

$$\underset{\text{Pyruvic acid}}{CH_3CO\ COOH} \xrightarrow{\text{carboxylase}} \underset{\text{Acetaldehyde}}{CH_3CHO} + CO_2$$

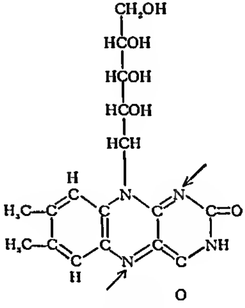
In order to act, carboxylase requires the presence of a coenzyme, called cocarboxylase, and shown to be thiamine pyrophosphate Thus, the need for thiamine in carbohydrate metabolism is evident

RIBOFLAVIN OR VITAMIN B_2

Vitamin B_2 was not recognized as a distinct entity for some time after the discovery of the vitamin B complex After the early separation of the original vitamin B into two parts (B and G) it was found that the B portion was thiamine or B_1 It was soon discovered, however, that the so-called "vitamin G" consisted of many factors and for a time they were all included under the general term, B_2-complex We no longer have a vitamin G, the term having been discarded, but in its place we have B_2, B_3, B_4, B_5, B_6, and other factors, some of them known by a chemical name as well

Riboflavin is a fluorescent pigment first found in milk and for a time called lactoflavin Later, however, when it was learned that ribose formed part of its molecule the vitamin received its present name

It has been isolated and synthesized, its empirical (simplest possible) formula is $C_{17}H_{20}O_6N_4$ and its molecular structure is shown in the following formula



Riboflavin

Its activity as part of an oxidation reduction system is owing to the presence of the two nitrogen atoms in the positions indicated by the arrows Riboflavin is heat stable provided the food containing it is acid It is destroyed rapidly in alkaline solution on exposure to light, especially ultra violet light, this is one means of obtaining for experimental purposes, a food deficient in this vitamin

Riboflavin is found in liver, kidney, egg white, heart, lean meat, fresh milk, and greens. The bodies of animals never give up all of their riboflavin content; even the bodies of those having died because of the deficiency contain at least one third of the normal amount.

In 1932, Warburg and Christian reported the presence of an oxidation enzyme obtained from yeast. It was a yellowish fluorescent compound, soluble in water, to which they gave the name "yellow enzyme." Upon isolation this compound has proved to be a flavoprotein containing riboflavin. Flavoproteins consist usually of riboflavin in combination with a protein and phosphoric acid.

Evidently they are present in all body cells taking part in the chain of reactions that occur during oxidative metabolism in cells.

Deficiency of Riboflavin

Lack of riboflavin in humans leads to many symptoms.

There may be a general reddening of the eye due to vascularization affecting the conjunctiva including the cornea, with the result that the person suffers from photophobia. *Cheilosis* makes its appearance; this is a condi-

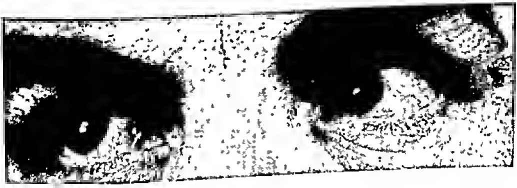


FIGURE 256

Circumcorneal vascularization caused by riboflavin deficiency. (Reproduced by courtesy of Parke, Davis and Co.)

tion marked by the presence, especially at the corners of the mouth, of fissures that are often bloody; the eyes and tongue may also become affected.

So-called "shark-skin," a dermatitis especially of the scalp, neck, face, and ears, may develop, accompanied also by a retardation in growth.

All of these symptoms may disappear by feeding riboflavin.

Requirements

Riboflavin is required by practically all animals, as well as some of the lower plants—yeast, molds, and bacteria, for example Its status in the protozoan phylum is as yet undetermined

Humans develop a deficiency in this vitamin in spite of the excellent sources in nature It is believed however, that inadequate supplies are present only in the diet of those with exceedingly abnormal eating habits Some of the vitamin is evidently synthesized in the intestinal tract, but as in the case of thiamine, the quantity found there and absorbed by the body is insufficient for human needs The diet should be supplemented so that at least a daily intake of 1 6 to 2 6 mg is obtained along with a daily diet of 2500 to 4500 calories, respectively

The Fundamental Action of Riboflavin

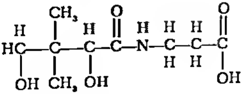
Riboflavin, as a component of flavoprotein, has a fundamental action concerned with oxidation reduction A flavoprotein, consisting of riboflavin a protein and phosphoric acid, is present in most living cells evidently essential as an important cog in the chain of reactions known to occur during cellular oxidation Riboflavin is the prosthetic or active group, acting not so much as an enzyme, but as a hydrogen acceptor and donator Evidence indicates that, in the cytochrome cytochrome oxidase type of mechanism flavoprotein accepts hydrogen ions from the coenzyme and gives them up to cytochrome However, it has also been suggested that this substance can actually bring about the union of the active hydrogen, being passed to it by the coenzyme, and molecular oxygen, no oxidase being needed There is still much to be learned concerning the part played by the flavoproteins in oxidation reduction

PANTOTNENIC ACID OR VITAMIN B_3

Pantothenic acid was isolated as one of the factors in the B complex in 1933 Although it is particularly valuable to yeast growth its involvement in human nutrition is still controversial Its deficiency in the diet of chicks produces a dermatitis which can be cured by feeding the vitamin Hooded rats on a diet deficient in pantothenic acid suffer a loss of fur pigmentation Since calcium pantothenate corrects this condition it has been called the anti gray factor in rats

Bound with protein in many types of animal tissues, vitamin B_3 is especially abundant in the liver and kidneys Rice bran is a rich source of supply, and some molds and bacteria produce it

It has the following chemical structure



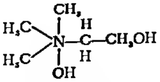
Pantothenic acid

CHOLINE OR VITAMIN B₄

We have already been introduced to one of the derivatives of choline acetylcholine (page 180), the chemical agent responsible for impulse transmission of parasympathetic and certain other nerves to effector systems

Choline is related also to fat metabolism Its necessity appeared as an aftermath of the researches on insulin by Banting and Best A depancreatized dog develops a condition of fat infiltration of the liver This, it was soon discovered, is not due to insulin deficiency but rather to an alteration in the nature of fat metabolism itself within the liver The phospholipids, lecithin and sphingomyelin, are normally formed in the liver from choline and fatty acids Both phospholipids are extremely important in most tissues In the absence of choline absorption (as occurs in a depancreatized animal, because of the loss of several digestive enzymes), these lipoids cannot be formed by the liver cells Hence the fatty acids form fat with glycerol and this is stored in the liver The liver cells are evidently unable to dispose of it If choline is added to the diet, the fat begins to disappear

Choline, a colorless crystalline substance, is very hygroscopic, with a marked tendency to absorb carbon dioxide It is not soluble in fat solvents It has the following structure



Choline

The fundamental action of choline is not known A question might be raised as to its inclusion among the B vitamins As far as we know at present, its importance lies in its ability to be incorporated into the lipoid

molecules mentioned above and into the neurohormone, acetylcholine. There is some evidence for choline having an important role in the formation of certain amino acids.

NIACIN, NICOTINIC ACID, P-P FACTOR OR VITAMIN B_5

Niacin, or vitamin B_5, known for many years as a derivative of nicotine, is sometimes called the pellagra-preventing, or P-P factor, since its absence causes the deficiency disease, pellagra. The term niacin is frequently used because of the possibility of confusing the term nicotinic acid with nicotine.

Free niacin is not found in living cells but is excreted as such in the urine. Although it is not stored in any great quantity in the body, the liver, adrenal glands and lens of the eye contain substantial quantities. Small amounts are found in milk, wheat germ and yeast. Naturally, since it is required by all cells for oxidation, it is present to some extent in all tissues, in the form of nicotinamide.

Considerable research was done in the 1930's in an attempt to discover the vitamin essential in preventing "blacktongue" in dogs, a condition analogous to pellagra in humans. Nicotinic acid and one of its derivatives, nicotinamide, were found to cure both. Nicotinic acid has the following formula:

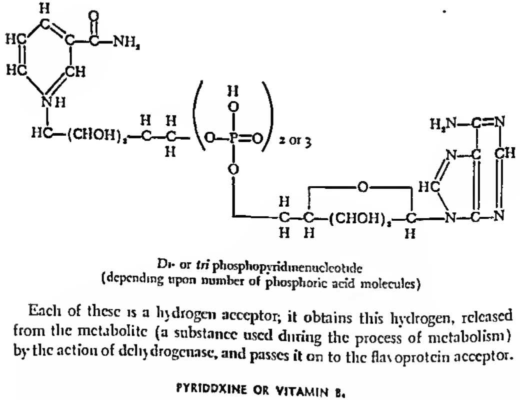
FIGURE 257

Pellagra with bilateral dermatitis (Reproduced by courtesy of Parke, Davis and Co.)

The amount of this vitamin required in the human diet is still unknown, but from 10 to 20 mg. daily is evidently a substantial quantity offering good prophylaxis against pellagra.

Fundamental Action of Nicotinic Acid

Nicotinic acid is another of the vitamins that lends itself as a prosthetic group in a substance the fundamental action of which is important in the oxidation-reduction system of a cell. As already pointed out, it is not found in a free form within cells but is combined, as nicotinamide, with phosphoric acid, adenylic acid and two molecules of ribose. Two or three molecules of phosphoric acid may be involved. If two are present, the substance is called coenzyme I or diphosphopyridinenucleotide, whereas if three are present it is called coenzyme II or triphosphopyridinenucleotide with the following basic molecular structure:



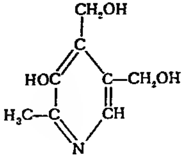
Di- or *tri* phosphopyridinenucleotide
(depending upon number of phosphoric acid molecules)

Each of these is a hydrogen acceptor; it obtains this hydrogen, released from the metabolite (a substance used during the process of metabolism) by the action of dehydrogenase, and passes it on to the flavoprotein acceptor.

PYRIDOXINE OR VITAMIN B_6

The importance of pyridoxine in human metabolism is still questionable, but it is definitely needed by the rat, chick, dog, and pig. Lack of this vitamin causes a dermatitis, attended by swelling and ulceration involving the feet, paws, and ears, and the areas about the nose, mouth and eyes, to

appear in these animals These conditions are definitely counteracted by the addition of pyridoxine to the diet The molecular structure is as follows



Pyridoxine

Pyridoxine has been found in most common foods Wheat germ, seeds, legumes, muscle, liver, kidney, and heart are good sources Many common species of bacteria, including those in the intestines, synthesize it also, which may explain the difficulty in producing the deficiency symptoms artificially Much remains to be done before the physiological action of pyridoxine is entirely understood However, evidence indicates that it acts as a coenzyme which is important for transaminations (transfer of the $-NH_2$, or amine, group from an amino acid to another compound) and certain decarboxylations (removal of the —COOH, or carboxyl group) Thus the material may be quite important in the metabolism of amino acids and fatty acids

FOLIC ACID OR PTEROYLGLUTAMIC ACID

Folic or pteroylglutamic acid, a recently isolated member of the B group, is found in leaves of green plants and in the liver and kidney of mammals Its biological action is not yet fully understood but it is probably associated with the normal production of nucleic acids Bacterial action produces it in the intestine of humans as well as other mammals with the result that one does not usually suffer from a deficiency

Absence of this vitamin in the diet of young chicks retards growth, and leads to an anemic condition If pure folic acid is given to them, the symptoms disappear

VITAMIN B_{12}

Vitamin B_{12} is perhaps the most recently discovered of the important vitamins Its discovery has aided greatly in clarifying the confusion that has existed in reference to pernicious anemia and its causes

In the chapter on blood physiology it was pointed out that a substance important for red blood cell production is stored in the livers of healthy individuals. This substance, sometimes called the antianemic factor or the erythrocyte maturing factor, is formed by the action of an intrinsic factor (occurring in gastric juice) on an extrinsic factor (taken with food).

It is now thought that vitamin B_{12} is both the extrinsic factor and the erythrocyte maturing factor. This conclusion is based on the fact that, if vitamin B_{12} is fed to a patient suffering from pernicious anemia, it has no effect, but, if it is injected, it is highly effective in stimulating formation of red cells.

Further research has shown that vitamin B_{12}, given orally, together with gastric juice from a normal individual, is also highly effective in production of red cells. Evidently, the intrinsic factor, a protein produced by the mucus secreting cells of the gastric glands, facilitates absorption of vitamin B_{12}.

Vitamin B_{12} is apparently synthesized to some extent by bacteria in the large intestine; however, since it is absorbed only in the upper small intestine, and since the intrinsic factor is necessary for this absorption, the vitamin produced in this manner is of no value to the individual.

Although the chemical structure of B_{12} has not been ascertained, as yet, it is known that cobalt is an essential part of its molecule. The best source for vitamin B_{12} is liver.

OTHER VITAMINS FOUND IN THE B COMPLEX GROUP

A number of other materials are sometimes listed with the B complex group, although in many cases, a definite need for these substances is difficult to demonstrate in humans.

Citrin (vitamin P), sometimes included in the B group, is a substance evidently contributing to the normal condition of the walls of small blood vessels, its function thus being closely associated with vitamin C. Persons suffering from capillary fragility, a condition in which pin points of hemorrhages appear in subcutaneous areas, may benefit by administration of this vitamin. Some controversy exists still concerning its exact chemical nature, but it probably consists of several substances.

Inosital, biotin, and para aminobenzoic acid (PABA) are all materials for which certain microorganisms may have a specific need, but which may play roles of lesser importance in higher forms of life. Inosital, the "antialopecia factor," since it seems essential for maintenance of hair in mice, also may be concerned with normal fat metabolism. Although it has not been demonstrated successfully that insects need inosital, insecticides closely

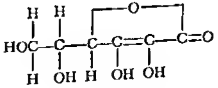
resembling it in molecular structure, and thus, possibly being able to replace inositol in the metabolism of cells, are highly effective.

Biotin also may be concerned in some way with fat metabolism. In this case, excessive biotin intake may cause excessive fat deposition in the liver, a condition not corrected by the administration of choline.

PABA is a proven requirement for growth of many bacteria. Here we see the relation of a required metabolite and a poisonous material. For example, sulfonamides, one of the 'sulfa' derivatives, owe their action to the fact that their molecule is so similar to that of PABA that they will actually displace PABA in bacterial metabolism. Thus, if bacterial growth is suppressed, the natural body defense mechanisms may be effective in destroying the microorganisms. The need for PABA by higher forms of life is still questionable.

ASCORBIC ACID OR VITAMIN C

Vitamin C, as many of the other vitamins, was discovered through the appearance of the deficiency disease. *Scurvy*, known and recognized for centuries, heretofore was especially liable to make its appearance during extended sea voyages. Vitamin C was first isolated, in 1928, from oranges, lemons, cabbages, and the cortex of adrenal glands, but its chemical nature was unknown at that time. Later (1932) it was shown to have a high degree of antiscorbutic potency. It was soon synthesized and the following formula given to it:



Ascorbic acid

Ascorbic acid is a comparatively strong organic acid, soluble in both water and alcohol, and readily destroyed by heat and oxidative processes; therefore, prolonged boiling, drying, or ageing of foods will reduce the ascorbic acid content. If foods are heated in the absence of oxygen, ascorbic acid is not destroyed. Its oxidation reduction powers are outstanding among its characteristics.

The richest sources of vitamin C are the citrus fruits, tomatoes, cabbage, green peppers, kale, spinach, and other greens. It is more concentrated in human milk than in cow's milk. It is stored to some extent in the human

body, the adrenal cortex, crystalline lens, corpus luteum, and the pituitary gland containing the largest amounts

Contrary to the usual effect of canning, when tomatoes are canned they retain large quantities of vitamin C There are several reasons for this (1) the initial concentration of vitamin in tomatoes is high, (2) the high acidity of tomatoes protects the vitamin against heating and oxidation, and (3) because of the acidity, the heating need not be so drastic as in canning other foods

Ascorbic Acid Deficiency

Many months elapse before the symptoms of scurvy appear as the result of a vitamin C deficient diet This disease seems to be confined to the guinea pig, man, and other primates, the lower mammals, for example rats, apparently being able to synthesize their own supply

The essential change during the onset of scurvy seems to be a weakening of the capillary walls, resulting in hemorrhages in various structures As corbic acid is essential for the maintenance of the normal consistency and the formation of the "intercellular cement" If the supply of this vitamin is inadequate, the cement weakens allowing the cells of the capillaries to separate

It is associated with the formation of collagen (the "ground" substance or matrix in which cells are imbedded) in connective tissues, cartilage, bone, and dentine Its mode of action is still unknown but probably it is involved in oxidative metabolism, although no good evidence exists in favor of this theory Some evidence indicates that ascorbic acid may be associated with immunological processes

The signs of scurvy may be listed (1) hemorrhages of the mucous membranes of the mouth, gastrointestinal tract, subcutaneous tissues, and muscles, and in the joints, (2) spongy, swollen, red gums becoming ulcerated and, in severe cases, gangrenous, (3) loose teeth, (4) anemia, (5) pains in the bones, spongy because of the withdrawal of calcium, (6) edema, (7) sore joints, (8) separation of the epiphyses, especially in young children, (9) decrease in oxygen consumption, (10) pigmentation of the skin, (11) sterility, and (12) general muscular weakness

Requirements

Compared with that of other vitamins, the requirement for vitamin C is rather high—a minimum daily dosage of 75 to 100 mg Being a threshold substance, it is not excreted in the urine if present in the blood below a certain level The blood "saturation" depends, in turn, upon the require-

FIGURE 258

Scurvy in young child (Reproduced by courtesy of Parke Davis and Co)

ments of the tissues If they are already saturated most of the ingested vitamin will be lost in the urine otherwise it will be retained It is said that the ascorbic acid in the diets of most humans at best is very little above the level at which the early symptoms of scurvy begin to appear

VITAMIN D OR THE ANTIRACHITIC VITAMIN

There are about ten D vitamins but only two of them are of special importance to man Vitamin D prevents the condition known as *rickets* in infants and *osteomalacia* in adults It exerts its action by its effect on calcium and phosphorus metabolism Naturally before the discovery of the antirachitic vitamin rickets was thought to be caused by a deficiency in calcium or phosphorus or to a wrong proportion of these elements in

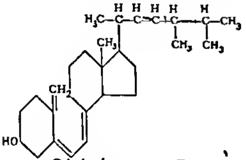
the diet It was soon evident, however, that a diet completely adequate in calcium and phosphorus but lacking in the vitamin, will result in rickets unless the body itself is able to produce its own supply

Sunshine has long been recognized as a preventative for rickets Children having liberal access to sunlight usually do not develop the disease, those suffering from rickets may overcome the condition if given proper exposure The ultraviolet is the important range of the spectrum, and since more of these rays reach us in the summer months than in the winter, naturally, if one is exposed to these rays directly, the sunshine is most effective in the summer These rays are absorbed by ordinary window glass although some recently developed types of glass are more transparent to ultraviolet Quartz is entirely transparent, but because of its cost it has not been used to any great extent There are now on the market rather inexpensive 'sun lamps that provide an excellent source of ultraviolet light during the winter months, and for the stay at home during the summer The two types of D vitamins that are of use to humans are vitamin D and vitamin D_3 (the original vitamin D_1 being a mixture of these, the use of the term has been discontinued)

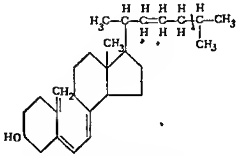
Vitamin D is produced by the irradiation of *ergosterol*, sometimes referred to as *pro-vitamin D* Ultraviolet rays change it to *calciferol* or D which is sold under the name of *viosterol*

Vitamin D_3 is formed by the action of ultraviolet on 7 dehydrocholesterol, a sterole occurring abundantly in the skin Thus adequate exposure to sunlight should ultimately supply the body with sufficient vitamin D_3 This is the chief type of vitamin found in fish liver oils

The formulae for these are as follows



Calciferol or vitamin D_2



Activated 7 dehydrocholesterol or vitamin D_3

Eggs and fish liver oils are the best sources of vitamin D Liver oils of the tuna, swordfish, halibut, and cod are rich in this vitamin Mammalian liver, on the other hand, is a poor source The antirachitic properties of

dairy foods, although usually quite low, still are more active than those of most other foods *Humans and other mammals may form a sufficient* amount of vitamin D for their own needs by the action of actinic rays on the skin, especially during the summer months Because of the poor supply of vitamin D in the foods we eat, the diets of young children should be fortified with the vitamin in concentrated form

FIGURE 259

Two types of deformities that make their appearance in vitamin D deficiency (rickets) A knock knees B bowed legs (*Reproduced by courtesy of Parke Davis and Co*)

Vitamin D Deficiency

As already noted, *the deficiency of vitamin D in the diet of young children* leads to the condition called rickets, characterized by defective ossifica

tion, owing to a disturbance in the calcium phosphorous metabolism. Consequently, various deformities, such as bowlegs, knock knees, malformation of the chest, curvature of the spine, enlargement of the epiphyses (the ends of the long bones), and poor development and calcification of the teeth, may make their appearance. In the adult, a deficiency in vitamin D causes the bones to lose calcium and phosphorus, and as a result become soft—a condition known as *osteomalacia*.

Factors Related to Occurrence of Rickets. In young children, a supplemental supply of D should be included in the diet, and, at the same time, calcium and phosphorus needs should not be overlooked.

Age and rate of growth are factors, in that the young child who is growing, especially if he is growing rapidly, is more susceptible to the disease than the older child who, although he also may be growing rapidly, usually has greater access to the rays of the sun. *Premature infants* are more apt to show symptoms of this condition than those born normally. This is understandable when one considers that 80 per cent of the calcium supply is stored by the fetus during the last three months of intrauterine life. Thus, if it is born before term, the infant has a deficiency in calcium.

The season of the year has already been mentioned as an important factor. Exposure to the summer sun is more effective than exposure during any other season.

Human Requirements

The amount of vitamin D needed to supply the body is very small. About 400 international units per day seem to be sufficient for the adult, although much greater quantities (up to 800 I.U.) should be given to very young children. The international unit for vitamin D is 0.000025 mg., therefore, 0.01 to 0.02 mg. per day are adequate.

In recent years, there has been some suggestion that vitamin D might possibly control arthritis with the result that, at times, enormous doses have been prescribed. Care should be taken, however, in resorting to such excessive doses even though the lethal dose is some 6000 times the rickets-preventing dose. Evidently, doses of about 60,000 I.U. or above may cause deposition of calcium and phosphorus in tissues other than bone.

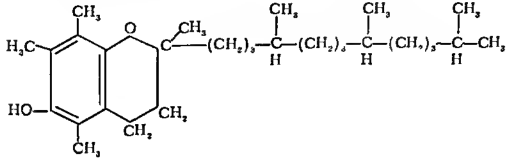
Fundamental Action of Vitamin D

The mode of action of vitamin D is not exactly known, but it has been established that, if the body suffers from a deficiency in this vitamin, very little, if any, calcium and phosphorus are absorbed through the intestinal wall, the major portion being excreted with the feces.

TOCOPHEROL OR VITAMIN E

There are actually three types of tocopherols in nature—alpha beta, and gamma The alpha tocopherol sometimes called the antisterility vitamin, is by far the most important

It is most abundant in wheat germ oil but occurs in so many foods that humans very seldom suffer from a lack of it in the diet Alpha tocopherol although insoluble in water, is soluble in fat and fat solvents It is now produced synthetically and has been given the following structure



Alpha tocopherol or vitamin E

Vitamin E Deficiency

It is still a question as to whether any great change takes place in humans who may experience a low tocopherol content in their bodies

Its absence has a definite effect upon rats resulting in failure to reproduce normally A progressive loss of fertility is apparent in the male rats the spermatozoa first losing their motility and later not even being produced The male soon loses the sex instinct also In female rats suffering from vitamin E lack implantation of the ovum occurs, but the embryos do not develop and are resorbed

There have been some claims to its usefulness in humans as a factor in overcoming habitual abortions but much more evidence is needed before such observations may be accepted as proof for vitamin E need

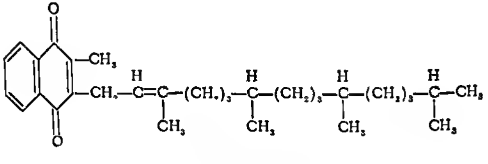
VITAMIN K OR THE ANTIHEMORRHAGIC VITAMIN

The effects of the deficiency of the antihemorrhagic vitamin were first observed on young chicks When fed an ether extracted diet (such as fish meal) about 50 per cent of them died bleeding as a result of a prolonged clotting time The increase in clotting time was found to be caused by a low prothrombin level in the blood If the affected chicks were fed the fat soluble factor which had been removed from the diet by ether the

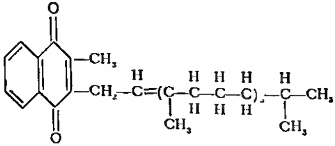
prothrombin level was again increased so that clotting occurred normally Dam and others called this new factor the *Koagulation* vitamin, which was abbreviated to vitamin K

Vitamin K is present in green leafy vegetables, alfalfa being an especially rich source It has been found also that certain types of bacteria, including those that dwell in the intestines of animals, can synthesize a factor which is antihemorrhagic, in that it acts like vitamin K in producing prothrombin in the blood

The vitamin found in alfalfa, designated as vitamin K_1, is a light yellow oil at ordinary temperatures That produced, during bacterial putrefaction, vitamin K_2, is a yellow crystalline solid These vitamins, synthesized in the laboratory as are other antihemorrhagic substances of far greater potency than the naturally occurring vitamins, have the following structures

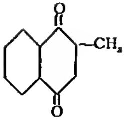


Vitamin K_1 from alfalfa



Vitamin K_2 from bacterial action

Various water soluble forms have been prepared One of the synthetic K vitamins is *menadione* which is 2 methyl 1, 4 naphtha quinone, with the following structural formula



Menadione

It is about three times more potent than either of the naturally occurring vitamins K

Vitamin K Deficiency

A deficiency of vitamin K is difficult to obtain in humans as well as in most other mammals because *bacteria in the intestinal tract can synthesize* it, and it is immediately absorbed through the intestinal wall Under certain conditions, however, the human body does not receive a sufficient supply For example if *bile secretion into the intestine is hindered or blocked* the vitamin is not absorbed This is true for all fat soluble vitamins (A D E, and K), since they must first be emulsified by the bile salts Jaundice resulting from blocking of bile secretion therefore will cause *hypoprothrombinemia* the term given to a hemorrhagic disease characterized by a low prothrombin level

The hemorrhagic disease found in some newborn infants has proven to be the result of vitamin K deficiency The bacteria which produce vitamin K are lacking from the intestinal tract at birth and they do not become sufficiently established for several days Even normal infants are said to show a very low prothrombin level on the second third or fourth day after birth because they do not get the mother's milk containing the vitamin until the fourth day and it is not yet produced in their intestines in appreciable amounts until then The prothrombin level depends upon the vitamin K intake of the mother before the birth of the child

It is now considered good practice to give an expectant mother vitamin K especially during the last several weeks before parturition This ensures a higher prothrombin level in the infant when it is born if the level is low, a slight cut could cause the death of the infant Often the vitamin is also given directly to the infant

Human Requirements

The human requirement is actually very low In normal adults, very little is required aside from that already found in the intestine In young infants, it has been found that 1 microgram (0 001 mg) daily suffices to hold prothrombin at a normal level However, as a safety measure much more than this dosage is usually given

Action of Vitamin K

The mode of action of vitamin K in the body is not known After entering the blood stream it is carried to the liver where in some manner it stimulates production of prothrombin Certain substances that may occasionally get into the diets of animals antagonize this action Bleeding disease of cattle for example occurs because of the presence of dicoumerol or related compounds in their food usually decayed clover contains large quantities of dicoumerol which prevents the formation of prothrombin despite the presence of a normal supply of vitamin K

ADDITIONAL READING

Evans E A *Biological Action of the Vitamins* (University of Chicago Press 1942) General discussions of vitamin functions and animal deficiencies
Wald G The Photoreceptor Function of the Carotenoids and Vitamins A *Vitamins and Hormones* I 195 1943

34

The Digestive System

DIGESTION AND ABSORPTION OF FOOD IN INVERTEBRATES

A VARIETY of structures and methods for digestion and absorption of food occurs in the invertebrates

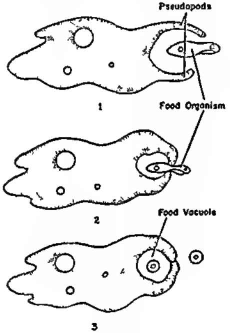


FIGURE 260

Food vacuole formation in an amoeba

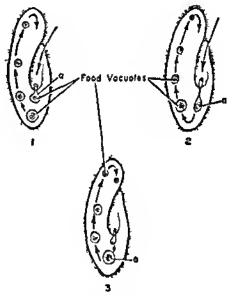


FIGURE 261

Successive stages of food vacuole formation and digestion in a paramecium A formation and pinching off of food vacuole

Some protozoans possess specialized structures, such as the gullets of ciliates and flagellates for food procurement and food ingestion In many cases, however no special organelles are present Amoebae, for example, merely flow around a food organism (Figure 260), thus forming a vacuole in which it is killed and digested Fundamentally, this is the same type of process occurring in the ciliates at the end of the gullet the food is collected into a pocket which from time to time, pinches off to form a food vacuole

In the vacuoles of both amoeboid and ciliated species the food organism is soon killed and gradually digested This is followed by absorption of the digested materials into the general protoplasmic mass

In the amoeba any undigested particles are removed by simply being left behind as the organism flows or moves about in paramecia they are removed by excretion through a special anal pore

This type of *intracellular digestion* is also found in sponges, coelenterates and platyhelminthes In the nemathelminthes digestion is completed in the alimentary tract and the broken down foods are then absorbed into the body This is the same type of process occurring at higher levels of the animal kingdom Many individual differences are apparent but for the most part digestion and absorption in the simpler forms of life are quite similar to that in the human or other mammals

THE ALIMENTARY TRACT OF MAN

The alimentary or digestive tract of man is essentially a tube that runs through the body and is open at both ends The anterior opening is the *mouth* the posterior the *anus* Actually there are two anterior openings

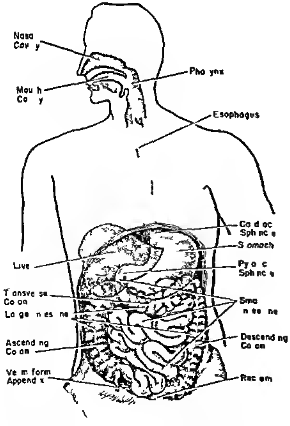


FIGURE 262

The human alimentary tract

the nose and mouth joining in the pharynx The tract is lined by a mucous membrane continuous with the outer integument at the lips nares and anal aperture Figure 267 shows its general appearance and the comparative sizes of the parts Many parts that are mentioned later in the text do not appear in this figure

THE BUCCAL CAVITY

The mouth opening leads into the *buccal* or *oral cavity* This cavity is surrounded by several structures the cheeks the hard palate the soft palate the tongue and the pharynx In the oral cavity the teeth are important structures in preparing food for digestion Two sets of teeth are formed during life the first set appearing soon after birth These are often referred to as milk teeth although primary teeth would be more appropriate They are lost during early childhood and a second or permanent set makes its appearance The teeth differ in certain respects in different parts of the mouth their structure depending upon the function they perform In the adult we find in each jaw four incisors two canines four bicuspids and six molars or thirty two teeth in the complete set In the primary set there are four incisors two canines and four molars in each jaw The total number in youth then is twenty We usually think of the incisors as functioning in cutting the canines in tearing the bicuspids and molars in grinding the food Tooth structure is primarily the same for all types the *crown* the *root* or *fang* and the *neck* or *cervix* being found in all An illustration of tooth structure is given in Figure 263

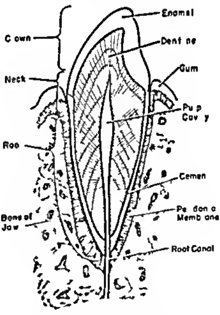


FIGURE 263

The human tooth and its relation to the jaw bone

The tongue surrounded in front and on the sides by the teeth is a very important organ in the preliminary digestive processes It functions in *mastication* or chewing and in swallowing Its function in tasting has already been discussed (page 210)

The salivary glands are exocrine glands (page 58) and pour their secretions into the mouth by way of ducts There are three pairs of salivary

glands: (1) The *parotid glands* lie at the angles of the jaws, a duct called *Stensen's* duct leading from each gland. The disease known as *mumps* results in the enlargement and inflammation of the parotid gland. (2) The *submaxillary glands* empty their contents by way of *Wharton's* ducts opening on the floor of the mouth. (3) The *sublingual glands* also open on the floor of the mouth by way of several ducts.

THE PHARYNX

The pharynx is the throat cavity into which the oral and respiratory passages lead. Both the oral and nasal cavities lead directly into the pharynx. The *eustachian* tubes (page 258) open here, and also the esophagus and trachea, tubes that lead from the lower part of the pharynx to the stomach and lungs, respectively.

The *esophagus* or *gullet* is about 10 in. long and is muscular. A cross section shows three distinct layers: a layer of mucous membrane lining the *lumen* or cavity of the esophagus, a middle connective tissue layer, and an outer muscular layer made up of both longitudinal and circular fibers. No glands connect with the esophagus, except the mucous glands scattered throughout the mucous membrane.

THE STOMACH

The stomach has three primary functions: (1) as a storage place for food, (2) as a digestive organ, and (3) as a producer of an 'intrinsic' factor that is essential for vitamin B_{12} absorption. The appearance of the stomach depends upon the tonus of its muscles. If it is empty, it is a rather small bag-shaped structure. Its larger domelike end, located on the left side beneath the diaphragm and extending upward above the opening of

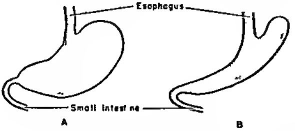


FIGURE 264

Variation in size of stomach. A, with food; B, empty.

the esophagus, is called the *fundus*; this whole area is known as the *cardiac* portion since it lies just beneath the apex of the heart. The opening of the esophagus into the stomach is closed by a sphincter or valve called the *cardiac sphincter*. The narrower end of the stomach connects with the

small intestine and is called the ***pyloric*** portion or *pylorus* The sphincter muscle between the pylorus and the intestine is known as the *pyloric sphincter* or valve The mucosa of the stomach is richly supplied with gastric glands which secrete the gastric juice

The stomach, like the esophagus, possesses a lining consisting of three distinct layers the innermost (the mucosa), the middle or connective tissue layer, and the outermost smooth muscle layer There are three layers of muscle—longitudinal, circular, and diagonal,—the thickenings of the circular layer forming the cardiac and pyloric sphincters

THE SMALL INTESTINE

Digestion is carried on almost entirely in the stomach and small intestine, especially the latter The small intestine about 20 ft long is further divided into (1) the *duodenum*, meaning twelve, in man it is about 12 in long, (2) the *jejunum* about 8 ft long and (3) the *ileum*, about 11 or 12 ft long

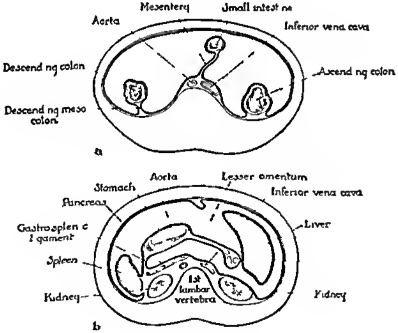


FIGURE 265

Cross section through abdominal region to illustrate peritoneal arrangement a lower abdominal region b upper abdominal region (From Greisheimer *Anatomy and Physiology* by permission of J B Lippincott Co)

The *peritoneum is the lining of the abdominal cavity, surrounding the* intestines and furnishing their attachment to the posterior wall of the cavity

The folds of the peritoneum in which are located the blood vessels, nerves, and lymphatics passing to and from the stomach and intestines are referred to as *mesentery*.

The pancreas, a large gland attached closely to the duodenum, has a double function, the secretion of pancreatic juice and the production of insulin The pancreatic digestive juice passes to the intestine through the pancreatic duct Immediately before entering the duodenum, this duct joins the bile duct at a point 2 to 4 in below the pyloric sphincter The liver is responsible for secretions (and excretions) that enter the intestine by way of the bile duct The intestine also has enzyme secreting glands within its walls

THE LARGE INTESTINE OR COLON

The large intestine is approximately 5 ft long and is subdivided into the *ascending colon, transverse colon, descending colon*, and the *rectum*

The ileum empties into the colon at the *caecum* (Figure 266) The junction is closed by the *ileocolic* or *ileocaecal sphincter*, which usually opens

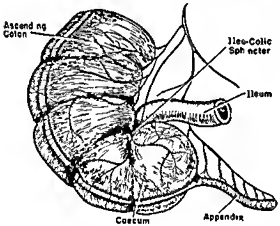


FIGURE 266

The caecum and its connection with the small intestine (ileum)

at the approach of intestinal contents The caecum is a blind pouch at the beginning of the ascending colon, ending in the *vermiform appendix*, merely a rudimentary structure in man The appendix is a narrow tube not as thick as the little finger and averages about 4 in in length The lower part of the descending colon makes an S shaped bend and is referred to as the *sigmoid flexure*

DETAILED STRUCTURE OF THE GASTROINTESTINAL TRACT

The gastrointestinal tract is the term given to the digestive and absorptive parts of the alimentary canal The structures throughout the alimentary tract, as already inferred, vary from one section to the next

The fact that the stomach has three layers of muscle tissue adds to its power to force the food into the intestine The mucosa has many longitudinal folds, or *rugae*, which increase its surface and allow for distension as the stomach is filled with food

Close examination shows (Figure 267) numerous openings covering the surface of the mucosa These are the pores of the tubular gastric glands, lined with several types of cells the *chief* cells, secreting *pepsinogen*, *parietal* cells, secreting acid and the *mucus secreting* (goblet) cells

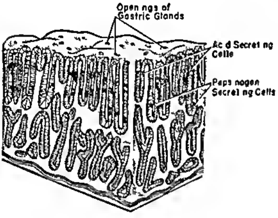


FIGURE 267

Section of stomach showing surface structure

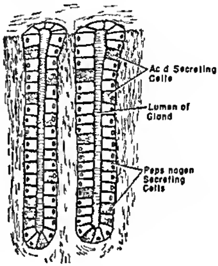


FIGURE 268

Glands of stomach indicating tubular structure and relative positions of secreting cells

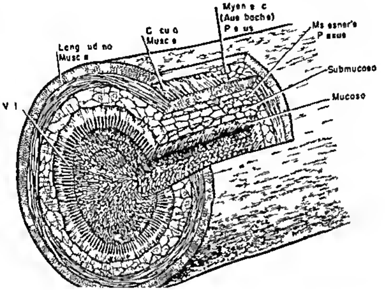
Only two muscular layers occur in the intestines, their arrangement in relation to the nerve plexuses and other structures being shown in Figure 269 There are also many folds within the intestine adding to its exposed surface area, but the most noticeable structures of the mucosa are the finger like villi which greatly increase its absorptive area

On close examination one can find the *crypts of Lieberkuhn* consisting of the intestinal glands that secrete intestinal juice An outer layer of *longitudinal muscle fibers* is separated from an inner layer of *circular muscle fibers* by a nerve network, called the *myenteric plexus*, or *Auerbach s plexus* This plexus, to which postganglionic fibers of the parasympathetic division lead, is the one chiefly concerned with motility of the intestine

A rather diffuse layer of smooth muscle cells, called the *muscularis mucosae*, lying immediately beneath the villi evidently aids in the shortening of the villi during digestion and absorption This diffuse layer of muscle

cells is innervated by another nerve network called *Meissner's plexus,* also found in the submucosa

The nerve supply reaches the gastrointestinal tract by way of sympathetic and parasympathetic fibers These are called *extrinsic nerves* whereas nerves within the walls of the tract (Auerbach's and Meissner's plexuses) are called *intrinsic nerves*



Some animals, such as the dog, do not chew their food, except when necessary in order to swallow it, the process of chewing not being essential to these animals. It is of interest to note, in this connection, that the muscular layers of the esophagus of the dog are made up entirely of striated muscle, as compared with those of humans, in which the upper two thirds of the esophagus consists of striated muscles, whereas the lower one third is composed of smooth muscle.

DEGLUTITION OR SWALLOWING

After the food mass is prepared the act of swallowing, initially a voluntary act, begins. The first stage of swallowing is accomplished by the tongue and cheeks pushing the food toward the pharynx. Once the food contacts the posterior wall, the second, involuntary, phase of swallowing begins, taking less than one second. The reflex causes contraction of muscles in the upper part of the pharynx and relaxation of those below, forcing the food into the esophagus. Other openings leading into the pharynx must necessarily be closed during this period or food might enter the nasal cavity or the lungs.

The passage leading to the lungs is closed by the lowering of the *epiglottis* and raising of the *larynx*, or voice box, found at the top of the trachea. The nasal passage is shut off by the elevation of the soft palate and uvula, respiration ceasing momentarily during this phase of swallowing. If food particles get into the nose they are usually removed by sniffing or "sneezing", those that get into the trachea or bronchi are removed by coughing.

The third phase begins when the food has entered the esophagus, through which it is carried to the stomach. This, also, is an involuntary action and is accomplished by a unique wavelike contraction called *peristalsis*, common throughout the alimentary tract. This movement results when a progressive contraction of muscles occurs immediately behind a food bolus, accompanied by a relaxation immediately in front of it. It has been found that a positive pressure equal to about 15 mm Hg is produced by contraction of the circular muscles above the bolus, and, because of dilation caused by contraction of the longitudinal muscles below a negative pressure equal to about −25 mm Hg is produced below the bolus. Thus, a total driving force equal to 40 mm Hg pressure carries the food to the stomach. It takes about ten seconds, more or less, to carry the bolus down to the stomach although fluids may pass directly through the esophagus within two to four seconds. Gravity alone does not carry liquids through the esophagus, this is accomplished chiefly by the direct effects of swallowing. When the food material nears the stomach the cardiac sphincter relaxes and opens, allow

ing it to pass through, and then contracts again In order to avoid the possibility of regurgitation, the sphincter must remain tightly closed when food is in the stomach, opening only at the approach of food

The nerve center concerned with swallowing is in the medulla Sensory or afferent neurons come to it from the walls of the pharynx, and efferent neurons leave it to stimulate the various muscles involved in the swallowing reflex Swallowing is difficult or impossible with injury or disease to the medullary center

MOVEMENTS OF THE STOMACH

The stomach, at least when first emptied of its contents, resembles a partially inflated bag, becoming much smaller as it gradually gains tone It functions as a reservoir for food, serving this purpose very well The two sphincters, one at each end, when constricted, isolate the stomach from the rest of the alimentary tract when it is discharging its digestive duties

The movements of the stomach and intestines can be examined by several methods, the X ray being very valuable for certain studies By this method, the passage of food mixed with barium sulfate, a compound opaque to X rays, can be followed through the digestive tract Another good method for studying digestive movements is that in which the subject swallows a balloon with a tube attached, the balloon is then inflated and the movements recorded by means of a tambour on a moveable drum Strips of smooth muscle from the stomach and intestine can also be attached to muscle levers and their action observed

As soon as food enters it, the stomach begins to increase in size, the peristaltic movements increasing at the same time, thus producing a churning effect One of the outstanding characteristics of the stomach is its ability to lose or gain capacity readily by change of tonus in order that it can adjust itself to exactly the right volume for the food that has entered it The peristaltic waves begin at about the middle of the stomach and move toward the pylorus In the human, it takes between eight and twelve seconds for each wave to pass to the pyloric sphincter, when food is in the stomach there is a recurrence about every two to three seconds with the result that several waves can be observed passing over the stomach at the same time These are the movements that churn the food and mix it with the gastric juice so that by the time it is ready to leave the stomach a semi liquid mass is formed It is called *chyme* which means juice The fundus merely serves as extra storage space and slowly forces the material to the active part of the stomach as needed

After a meal it usually takes three to four hours to empty the stomach the length of time naturally, depends on many factors The *consistency of food* is one factor if it is in a liquid state it leaves more rapidly than otherwise In fact, liquid leaves the stomach almost immediately The *quantity of food* is another factor as is the type of food Carbohydrates leave the stomach more rapidly than proteins and proteins more rapidly than fats However all of these foods are held until the duodenum is ready for them They are held back by the pyloric sphincter which opens only occasionally and allows some of the partly digested food (chyme) to flow into the duodenum

The regulation of the pyloric sphincter is still not thoroughly understood although at one time it was thought that it opened whenever the *pH* on the duodenal side was alkaline and that as soon as sufficient acid chyme had passed into it muscles of the pylorus were forced to contract closing the sphincter and not until the food again became alkaline on that side would it reopen It is true that acid on the duodenal side causes contraction of the pyloric sphincter but the acid concentration necessary to cause it is much higher than that found in the chyme It is doubtful that this is the only mechanism influencing pyloric sphincter function

Recent evidence seems to support the idea that the stomach empties itself by way of a reflex action (or hormone action) Receptors in the walls of the intestine may be stimulated by various foods or their products and cause more powerful peristaltic movements which force the food through the pylorus This would explain the difference in the time of emptying in the case of different foods For example fats slow the action because once in the intestine they are least effective in producing the reflex Proteins are slow in movement through the stomach because they (or their products) also have little effect on receptors in the walls of the duodenum causing an increase in movement carbohydrates are more effective However there is evidently another factor involved for hypertonic solutions of carbohydrates may be retained within the stomach until they are reduced by the gastric juice to isotonicity (that is a concentration similar to the concentration of materials in the living cells)

HUNGER

As mentioned previously (page 470) after the stomach empties itself it is still relatively large but gradually with the increase in tonus it becomes much smaller Vigorous contractions may set in some time later producing the uncomfortable feeling of hunger They may become so vigorous that

painful sensations—hunger pains, or pangs,—are experienced Possibly they occur in the empty stomach because the contraction takes place in an organ already in almost complete tonus

During a fast, one finds that these uncomfortable feelings pass off after a few days, at least, the feeling of hunger is not so intense

VOMITING

Vomiting or *emesis* is a reflex act resulting in the evacuation of the stomach The vomiting center is found in the medulla

Usually just before this act, a feeling of *nausea* is experienced and is associated with a dilation of the upper part of the stomach, including the cardiac sphincter, and contraction of the pyloric end If the condition leads to vomiting the abdominal muscles contract and, pressing against the stomach force its contents through the relaxed cardiac sphincter and up the esophagus The food can be ejected with considerable force In adults, the stomach does not empty itself by antiperistalsis, but in lower mammals and infants this is a factor

MOVEMENTS OF THE SMALL INTESTINE

The food takes about three to five hours to pass through the small intestine It is carried along by peristaltic movements, as is true for the entire alimentary canal Before it is pushed forward toward the colon, the food is mixed thoroughly by movements of the intestine that play no part in propulsion Two such nonpropulsive movements occur in the small intestine

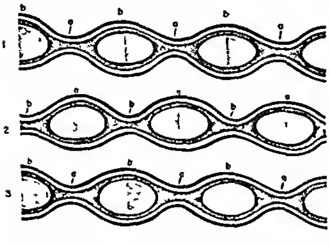


FIGURE 270

Segmentation in intestinal wall illustrating the successive contractions of different muscle groups At 1 muscle groups *a* are contracted and *b* are relaxed at 2 muscle groups *b* are contracted and *a* are relaxed at 3 same as at 1

1 *Rhythmic segmentation*, accomplished by local constrictions of the circular muscles They arise simultaneously at various and numerous points

along the intestine A diagram is used to illustrate this in Figure 270 These contractions appear at the rate of twenty or thirty per minute, each successive group of contractions occurring at different locations In this manner, the food is well churned and mixed with enzymes before it goes on to the lower part of the intestine This movement also aids in bringing the chyme, with digested materials, into direct contact with the absorbing surface of the intestine

2 *Pendular movements*, caused by contractions of the longitudinal muscles These contraction waves pass over rather short strips of muscle producing in this way a swinging motion similar to that of a pendulum They, also, result in a more thorough mixture of the chyme with the juices of the intestine

Segmentation and pendular movements occur without nervous stimulation They are, therefore, said to be *myogenic* in origin, that is, the contractions originate in the muscles of the intestinal walls

Peristalsis takes place intermittently as waves, traveling at the rate of one to two cm per second carrying the contents of the intestine with them They do not travel very great distances over the intestine but they appear at many places along its axis The nerves, at least the intrinsic nerves are necessary for peristalsis If the extrinsic nerves are cut peristalsis will continue, but it is found that orderly regulation of the contractions is dependent upon these autonomic nerves The *myenteric plexus*, therefore is very important in peristalsis Drugs such as atropine or nicotine, which paralyze these nerves, lower the tone and retard the contraction waves

Antiperistaltic waves that move toward the stomach may be found also in the small intestine They tend to keep the food up in the forepart of the small intestine until the digestible part of the food is absorbed

The villi in the intestine are in continuous movement By means of moving pictures it has been observed that they may move back and forth in a wavelike manner, occasionally shortening by means of muscular contraction This latter movement probably aids in forcing the lymph out of the lacteal into the larger lymphatic vessels The muscle cells of the *muscularis mucosae* produce these movements in the villi which return to their original position when the muscle cells relax The *ileocolic* or *ileocecal valve* separates the small intestine (ileum) from the large (colon) It is usually closed but when undigested or unabsorbed food matter reaches it, it opens, a reaction similar to that when food approaches the cardiac sphincter via the esophagus (page 475) The material that enters the colon from the ileum is in a liquid state The valve functions in the following ways (1) it prevents too rapid a movement of food from the small intestine to the

colon, and (2) it prevents regurgitation of fecal matter back into the small intestine.

MOVEMENTS OF THE LARGE INTESTINE

Very little usable food is left in the material that enters the colon—most of it has been absorbed and only indigestible and unabsorbable substances are present. The contents of the large intestine remain longer in it than in any other part of the alimentary canal. It may take as long as 24 hours for it to pass through. Movements similar to those of the small intestine (segmentation and pendular) are found in the colon, having the same function as in the small intestine. The waste material, like that of the small intestine, is liquid and it is here that most of the water is reabsorbed. Antiperistalsis occurs for a long time after the liquid mass enters the large intestine.

Soon after food is taken into the mouth a vigorous action appears in the colon due to peristalsis which is here referred to as *mass peristalsis*. The walls of the large intestine lose their segmentation and become smooth. Peristaltic contractions seem to be centered in the ascending and transverse colon forcing the fecal matter into the descending colon for disposal. The reflex producing the movement is called the *gastrocolic reflex*. If the contents reach the rectum there is a desire to *evacuate* or *defecate*.

DEFECATION OR EVACUATION

Defecation or evacuation is the final phase involving digestion and absorption of food in the alimentary tract.

The rectum ordinarily has a very low pressure and is usually empty. When fecal material is forced into it, the pressure may increase greatly

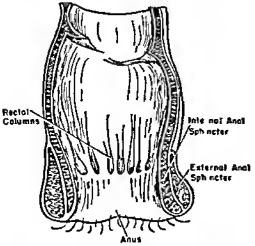


FIGURE 271
Structure of anus. The lower end of the anus and rectum has been spread apart.

A rise of only a few mm Hg pressure is detectable while a rise of 40 to 60 mm results in distress The increase in pressure causes an increase in strength and number of peristaltic waves in the colon The *internal anal sphincter* is then relaxed, while the *external anal sphincter* may be opened or kept closed voluntarily In defecation both sphincters are relaxed and the contents of the rectum free to leave The act may be aided by forcible contraction of the abdominal muscles and diaphragm to produce a positive pressure against the rectum and its contents in order to force the fecal matter through the opening The internal sphincter is composed of smooth muscle, the external sphincter of striated muscle

ADDITIONAL READING

Best, C H, and N B Taylor, *Physiological Basis of Medical Practice* (Baltimore Williams and Wilkins 1950), chs 43, 44 Mechanical aspects of digestion

Fulton, J F, *Textbook of Physiology*, 16th ed (Saunders, 1950), ch 46 General functions of the digestive system

35

The Secretion and Action of the Digestive Juices

SALIVA AND ITS FUNCTIONS

Saliva is a mixture of secretions from all three pairs of salivary glands (parotid submaxillary and sublingual) and has several functions

1 It has a *lubricating action* The food is prepared for swallowing by mixing it with saliva which softens the food mass and gives it a slick surface

2 It has a *solvent action* on foods soluble in water This of course, aids us in tasting foods which must be in solution in order to stimulate the taste buds

3 It has a *moistening* and *lubricating action* on the structures of the mouth which are essential to speech Speech would be difficult if not impossible with a dry mouth

4 It has a *cleansing action* on the mouth and teeth tending to keep them free of food material and thus diminish bacterial growth We give aid to this action by brushing the teeth

5 It is partly *excretory* in action Some of the heavy metals and drugs are excreted by way of the salivary glands

6 It *aids* in the *water balance* of the body in that it is a factor in the sensation of thirst Its effect upon the thirst receptors in the throat depends upon its consistency

If the water content of the body and blood is low the tissues do not receive a normal quota The salivary glands along with other tissues are therefore low in water content The saliva secreted by the glands becomes viscous thereby producing a sensation of thirst when it contacts the walls of the throat Thus, if one has access to water, he will drink it, and in this way increase the water content of the body

7 It has a *digestive function* in its action on starch and glycogen By hydrolysis, the enzyme *ptyalin* or *salivary amylase* breaks down these molecules into disaccharides Food does not remain in the mouth very long hence digestion is not significant here In the stomach if saliva is mixed

with the gastric juice the action of ptyalin is inhibited by the acid content However, the food taken during the latter part of a meal will remain for a time in the fundic region where salivary digestion can go on unhindered Very small amounts of maltase may be secreted also in saliva, it hydrolyzes maltose to glucose

The parotid glands produce a secretion high in enzyme content They are innervated by the parasympathetics, via branches of the ninth cranial or glossopharyngeal nerves Sympathetic fibers run to the blood vessels of the gland and are vasoconstrictors Thus, stimulation of the glossopharyngeal branches causes a copious flow of a watery secretion, whereas stimulation of the sympathetic has no effect upon secretion, although there is a decrease in secretion granules within the glandular cells

The submaxillary and sublingual glands also are innervated by the parasympathetic division, but by way of the *chorda tympani*, a branch of the seventh cranial or facial nerve In both of these glands stimulation of the parasympathetics results in a watery secretion high in enzyme content but stimulation of the sympathetics (which have no fibers leading directly to the salivary cells) causes a greater secretion of mucin which tends to increase the viscosity of the saliva

Saliva normally has a slightly acid reaction, *p*H 6 3 to 6 85, and is about 99 per cent water, the remaining 1 per cent consists of enzymes, mucin salts, bacteria, and other cells About 1000 to 1500 cc are secreted in 24 hours, most of it being carried down the alimentary canal

Its secretion is brought about only by reflex action This reflex may be of a conditioned or unconditioned type In the latter case, the taste buds in the mouth are stimulated and, by reflex pathways, the salivary response is produced, in the former case, the reflex is built up through various associations in vision, smell, hearing and thought

GASTRIC JUICE AND ITS FUNCTION

Gastric juice functions in the digestion of food This was mentioned previously as one of the three functions of the stomach (page 475) The functions of the stomach as a digestive organ and as a storage place for food are not absolutely essential in mammals for the stomach can be removed partially or entirely without any serious effect on digestive processes after recovery is complete, if antianemic principle is fed to the animal or human Persons whose stomachs have been removed must eat less food but eat more frequently since there is a more limited storage space in the alimentary canal

The number of glands in the walls of the stomach has been estimated at

about 35,000,000. They are tubular glands, containing either two or three types of cells (page 473). The *mucus secreting* cells are found near the opening of the gland. The *parietal* or *acid secreting* cells occur in the body of the gland. The *chief* cells are present in the deeper parts of the gland and produce the precursor of pepsin, called *pepsinogen*. In general, these precursors are called *zymogens*.

The glands in the central region or body of the stomach usually have all three types present. In the pyloric end of the stomach, the glands have no acid secreting cells but chief cells and mucous cells are found.

The gastric juice is necessarily acid, since pepsin, which digests protein, is active only in highly acid solutions. In fact, pepsinogen is not activated until it comes into contact with hydrochloric acid (HCl) which changes it to pepsin. The optimum acidity for pepsin action is about pH 1.5. Pure gastric juice contains 98 per cent water, the enzymes *pepsin*, *rennin*, and gastric *lipase*, inorganic salts, and HCl in sufficient quantity to increase its acidity to pH 0.9 to 1.5. By the time this acid becomes mixed with food however, the acidity is much less—about pH 2.0 to 3.0.

The enzymes rennin, which curdles milk (that is, precipitates the protein casein), and lipase, which acts on fats, are not very effective in the gastric digestion of adults. Rennin is most active at pH 6.0 and does not act below pH 4.6; lipase is most active at pH 5.0. In infants, the gastric juice is not very acid, being nearer the optimum range for rennin action; in adults, this enzyme is practically useless, but the HCl alone would bring about the curdling of the milk. The effectiveness of the fat splitting enzyme is also questionable. Its action would be far greater in the intestines, where the food is emulsified to a greater extent than in the stomach.

The curdling of milk in the stomach is evidently necessary to prevent the fluid milk from passing directly through the stomach. The curd can then be acted upon by pepsin.

Studies of Gastric Secretion

One of the earliest studies on the secretion and action of gastric juice was made by the Italian, Spallanzani, in 1782. He found that the gastric juice of birds and humans 'dissolved' food, especially meat. Previous to his time such suggestions were unheard of, the prevalent belief being that some "vital influence" was necessary. Many believed also that millions of small worms attacked the food in the stomach and digested it. Evidently this notion developed because of the parasitic worms undoubtedly existing in the alimentary tracts of humans and other animals in those days.

These ideas were still held by many until the time of William Beaumont,

the physician responsible for much of the earlier knowledge of the movements and secretions of the stomach

At Mackinac Island in 1822, Beaumont was called upon to attend a French Canadian half breed by the name of Alexis St Martin, who had been shot accidentally in the side He stitched the edges of the stomach wall, which had been torn open by the gun shot, to the abdominal wall to make him more comfortable He expected the patient to die but to his surprise he continued to live although he had a large hole leading directly into his stomach Openings of this type are referred to as *fistulas*

Realizing the value of his patient, Beaumont took him into his home as his servant and assistant By looking through the hole in the abdominal wall, he could see the stomach move, and the gastric juice pour out of the glands, especially when food entered the stomach As a result of some very well organized experiments with his human guinea pig, he proved definitely that gastric juice is normally produced at all times, although in minute quantities between meals Samples of gastric juice, taken under different conditions, were found, on analysis, to contain high concentrations of hydrochloric acid

Beaumont's greatest difficulty proved to be the behavior of St Martin who had a taste for alcoholic beverages Sometimes he would disappear for months in the middle of an experiment However, in spite of his many difficulties, Beaumont published a monograph in 1833 entitled "Experiments and Observations on the Gastric Juice" which has proven to be one of the classics of physiology

Early in this century, Dr Carlson of the University of Chicago added greatly to our knowledge of gastric function by his observations made on a man with a similar fistula caused by an operation performed when his esophagus had closed following the accidental drinking of caustic alkali

Control of Gastric Secretion

Two natural methods control gastric secretions in the human stomach nervous control and hormonal control

The Russian scientist Pavlov, and his co workers, carried out most of the early investigations on *nervous* control of gastric secretions

The gastric glands are innervated by the parasympathetic division of the autonomic nervous system via the vagi, when stimulated, the vagi cause an increase in the secretion of acid and enzymes The sympathetic division causes vasoconstriction in the stomach mucosa and hence inhibition of secretion except that it may increase mucous secretion Pavlov demonstrated by means of an esophageal fistula (Figure 272) in dogs that the

presence of food in the mouth caused gastric secretion (a fact which Beaumont had not observed) This type of feeding is referred to as sham feeding because the food that the dog takes into its mouth and swallows

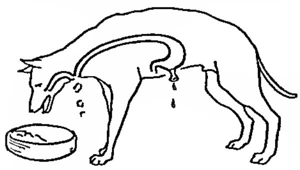


FIGURE 272

An esophageal fistula by means of which sham feeding experiments are carried out In this way Pavlov proved that the presence of food in the mouth initiated gastric secretion

passes out through the opening in the neck It never reaches the stomach yet this organ is activated reflexly so that there is an increase in secretion If the vagus nerves to the stomach are cut the stomach no longer responds to the presence of food in the mouth It is now known that sensory fibers from the taste organs lead to a center in the medulla where the impulses coming from them are transmitted to the vagal fibers and down to the stomach increasing its activity

The reflex is also set up by sensory fibers from the organs of sight smell and hearing and it is known that even the thought of food causes gastric secretion The stimulation affecting these organs is called *psychic* stimulation as compared to contact stimulation in the mouth The denervated stomach is not activated by any of these stimuli however gastric secretion continues if food is put into the lumen of the stomach This is caused by *humoral* or *hormonal* stimulation

Unpleasant experiences seem to hinder secretion in the stomach This is also true of emotional upsets such as fear anger or embarrassment Pleasant table surroundings are essential to proper secretion and digestion Family quarrels at the dinner table may cause indigestion Carlson has done much work on this problem He has shown that a large quantity of gastric juice is produced in humans during the process of eating but that it decreases soon after and that this secretion has a high concentration of pepsin

Gastrin

It has already been pointed out that contact of food with the stomach wall causes an increase in secretion This occurs even in a completely denervated stomach or in a transplant of gastric tissue far removed from the

stomach and placed in such a position as to form a pouch in order that secretion can be studied If the transplant is successful, a circulation is established and it is referred to as a stomach pouch If now the animal on which the transplant was made, is fed in the usual manner, the stomach itself secretes normally At the same time, in the stomach pouch, which has only a blood supply, no nerves, the glands begin to secrete The only way in which this activity could be initiated is by means of a chemical substance a hormone carried by the blood stream The glands within the pouch respond to the hormone even though they may be at some distance from the stomach

Certain substances in foods act on the stomach mucosa, causing it to produce a hormone called *gastrin* This hormone, absorbed into the blood, and carried to the gastric glands, stimulates them to greater secretion Some of it reaches the transplanted stomach pouch by way of the blood stream and has a similar effect on the secreting cells there Histamine has been found to have a very powerful influence on gastric secretion and, as a result, some investigators are inclined to believe that this is identical with the hormone gastrin

An "intestinal" phase of gastric secretion occurs also which is probably due to the production of a hormone If food is placed in the upper part of the duodenum of a dog, the stomach glands begin to secrete, although no food was present in the stomach or had come in contact with the mouth It is known also that if the intestinal chyme is drained off a rapid reduction in gastric secretion takes place

In summary, then, we can divide the gastric responses into 3 phases: (1) the *psychic phase* which requires a conditioning in the case of smell, sight or hearing but which is unconditioned in the case of contact or taste stimulation, (2) the *gastric phase* in which a hormone, causing secretion, is produced and (3) the *intestinal phase*

THE PRODUCTION AND ORIGIN OF HYDROCHLORIC ACID

The hydrochloric acid of gastric juice is evidently secreted by the parietal cells of the tubular glands In the glands of the middle portion of the stomach these cells occur in large numbers and it is here that the greater part of the acid is produced In the pyloric region no parietal cells are present, and the secretion is alkaline in action Also, chemical tests show a high concentration of chloride in the parietal cells This chloride is undoubtedly the source of that found in the HCl, in fact, it is known that the parietal cells show an acid reaction

How the HCl is produced is still a question No theory as yet advanced

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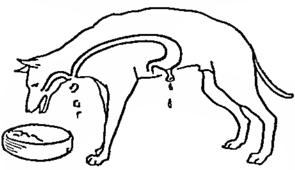

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is wholly satisfactory in explaining secretion of HCl Years ago it was suggested that the reaction which results in its formation also involves the acid phosphates

$$NaH_2PO_4 + NaCl \longrightarrow Na_2HPO_4 + HCl$$

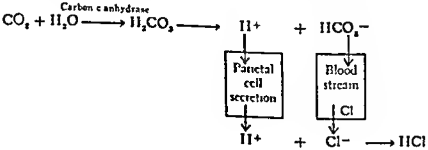
It was suggested also that the HCl is secreted into the duct of the gland while the alkaline phosphate passes back into the blood stream, increasing the alkalinity of the blood It is a fact that after the completion of gastric digestion, the urine becomes more alkaline This increase in alkali concentration in the blood is referred to as the "alkaline tide"

Another early idea proposed that HCl is formed by interaction of protein, containing many carboxyl groups, and sodium chloride The *Sodium Proteinate Theory*, as it was called, may be represented by the equation

$$\text{Protein COOH} + NaCl \longrightarrow \text{Protein COONa} + HCl$$

However, these two theories are thought to be too simple to explain a process seemingly as complicated as that for HCl formation

More recently, many new theories have been proposed in an attempt to explain this phenomenon One receiving much attention is that of Davenport which was presented in 1941 It was found that the parietal cells contain the enzyme, *carbonic anhydrase*, in greater concentrations than in red blood cells where it is important for transport of carbon dioxide Its function in this respect has been considered in Chapter 30 According to Davenport's theory, carbon dioxide, formed within the parietal cell is combined with water through the action of the carbonic anhydrase to form carbonic acid From this acid, the hydrogen ion is excreted by the cell and the bicarbonate ion moves into the blood capillaries As a result of the increase in blood bicarbonate, chloride ions leave the blood stream and, with the excreted hydrogen ions, form the HCl which is secreted from the gastric glands The reactions may be represented by the following



THE CONTROL OF ACIDITY IN THE STOMACH

The stomach can withstand high acidity, but sometimes certain types of foods or an emotional upset may cause too great an acid secretion If it is only temporary one may suffer no ill effects

Sometimes the stomach of an individual may continuously secrete large quantities of acid, producing *hyperacidity* or *hyperchlorhydria* There is no increase in the acidity of the gastric juice but an increase in quantity produced Duodenal or gastric ulcers and pyloric obstruction are almost invariably accompanied by hyperacidity

The question arises as to why the stomach does not digest itself, especially when the acid and pepsin content is high Ulcers are actually produced by partial digestion of the walls of the stomach It is true that the incidence of ulcer is greater in individuals with hyperacidity than others, but many suffer from hyperacidity and yet do not have ulcers If pieces of stomach tissue are placed in the intact stomach, they are digested just the same as any other protein However, if some other tissue is transplanted onto the wall of an active stomach and subsequently develops a blood circulation, it is not digested any more than the intact stomach wall

At death, especially sudden death, following a meal when there is a large quantity of gastric juice in the stomach, the stomach does begin to digest itself There is no satisfactory explanation to this problem Some have suggested the presence of an antipepsin in the walls of the gastric mucosa

A decrease in gastric acidity, *subacidity* or *hypochlorhydria*, occurs in many individuals without producing any apparent symptoms

Anacidity or *achlorhydria* is found in about 4 per cent of normal humans Symptoms may or may not appear Sometimes a persistent diarrhea is associated with it, which can be overcome by administering acid This condition appears in almost 100 per cent of patients with pernicious anemia Gastric cancer and gastric inflammation are also accompanied by this condition

DIGESTIVE PROCESSES IN THE STOMACH

When the food enters the stomach it is usually fairly solid, or perhaps somewhat pastelike in consistency When it leaves the stomach it is in a semiliquid to liquid condition, and is referred to as *chyme* During its stay in the stomach, gastric juice is added to the food (from 1000 to 2500 cc of gastric juice are produced daily) and changes begin to take place in the molecular structure of the food Proteins are hydrolyzed

to *proteoses* and *peptones* They are never broken down completely into amino acids, this is done in the intestine If some of the protein remains undigested there are proteolytic enzymes produced in the intestine which continue the protein hydrolysis The *carbohydrates* are in the form of *sugars* and *starch* Some sugar is usually included in the diet and some of the starch is acted upon by salivary amylase in the fundus and is hydrolyzed to disaccharides If maltose is present or formed later, the enzyme maltase will act also in the fundus to hydrolyze this sugar to glucose The extent of emulsification and digestion of fats in the stomach is very small compared with digestion in the intestine

All of these products undergo a mild trituration in the stomach and become thoroughly mixed The churning also is rather mild even though the contractions of the stomach appear vigorous This is easily noted when the diet consists of such foods as whole grapes that are not chewed or peas —they are excreted in the feces in practically the same condition as they were swallowed the stomach having very little effect on them

The chyme produced by the activity in the stomach, contains only partially digested proteins carbohydrates and fats, and is ready for further action in the intestine Periodically, portions of it pass through the pyloric sphincter into the duodenum

PANCREATIC JUICE AND ITS ACTION

Pancreatic juice is secreted by the *alveolar cells* of the pancreas It is carried by the pancreatic duct to the intestine into which it empties at the

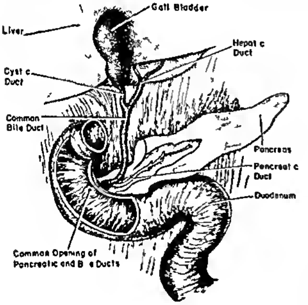


FIGURE 273

The pancreatic and bile ducts showing their union just previous to their entrance into the duodenum

same point as does the bile duct—just a few centimeters below the pyloric sphincter If observed before secretion has occurred the cells of the pancreas are found to contain large numbers of secretion granules Observation immediately following a meal shows the granules to have disappeared, the secretions have been thrown into the pancreatic duct

Every twenty four hours the pancreas produces about 800 cc of juice This fluid consists of about 98 per cent water and 2 per cent solids, chiefly enzymes It has an alkaline reaction and contains sodium carbonate and bicarbonate

The food coming from the stomach in the form of chyme must be further digested if it is to be absorbed Many enzymes which either initiate or continue protein, carbohydrate and fat digestion, are found in the small intestine Some of these enzymes are produced by the pancreas and others by the intestinal glands The bile contains no enzymes but it furnishes a medium aiding in the digestion and absorption of fats

Enzymes of the Pancreatic Juice

The pancreatic juice contains enzymes capable of carrying out partial or complete digestion of proteins, carbohydrates and fats All of these enzymes require a neutral or slightly alkaline condition for optimum action, the bile, pancreatic and intestinal juices contain sufficient basic salts to neutralize partially the acid chyme from the stomach During fasting the contents of the duodenum may approach an alkalinity of about *pH* 8 0 but during digestion of food due to the acid chyme from the stomach the contents may be very slightly acid (*p*H 6 6) nevertheless the enzymes still function well

Three proteolytic enzymes have been identified *Trypsin* acts upon natural proteins in a fashion very similar to pepsin and reduces them to proteoses and peptones As formed in the pancreas, it is in the inactive form, *trypsinogen*, and requires the presence of the enzyme *enterokinase*, produced by the intestinal glands, for its conversion to active trypsin However, minute traces of trypsin can cause a rapid conversion of more trypsinogen to trypsin *Chymotrypsinogen* also may act on proteins but only after it is converted to the active form *chymotrypsin* by the presence of trypsin Thus these two enzymes are dependent upon the presence of enterokinase for their proper functioning *Carboxypeptidase* acts upon polypeptides splitting off amino acids having a carboxyl group free at the end of the polypeptide chain

Pancreatic amylase acts on starch, hydrolyzing it to monosaccharides In this respect, it is similar to salivary amylase, but is more powerful since the

reaction is accomplished much more rapidly Small amounts of *maltase* may carry the digestive action on until monosaccharides are produced

Pancreatic lipase, known also as steapsin is a fat splitting enzyme requiring the aid of bile salts produced in the liver

Regulation of Pancreatic Secretion

Control of pancreatic secretion is partly nervous, partly hormonal If food is placed in the mouth the pancreas begins to secrete as a result of reflex stimulation, conditioned or unconditioned Sight, thought or smell are all included under conditioned stimuli as compared with contact stimulation in the mouth which is unconditioned By means of these reflexes, the intestine in the same manner as the stomach, is prepared for the reception of food The vagi innervate the pancreas direct stimulation of these nerves will cause secretion

The pancreas however even though denervated, continues to secrete as long as food comes to the stomach—a fact discovered in 1902 by Bayliss and Starling They found that when the chyme (containing acid gastric juice) entered the intestine, it caused the production of a hormone, called *secretin* This is absorbed into the blood stream and carried to the pancreas which is stimulated to greater secretion

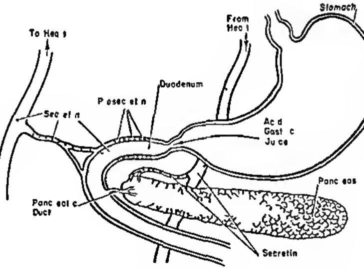


FIGURE 274

The production of secretin and its movement via blood stream to pancreas The action of HCl on prosecretin in duodenal wall produces secretin which is carried via blood stream to heart and finally back to pancreas where it causes digestive cells to produce pancreatic juice

Evidently this hormone, existing as *prosecretin* in the walls of the duodenum, is activated by hydrochloric acid

These same investigators also found that an acid extract of the duodenum when injected into the blood stream of a mammal causes greater secretion of the pancreas, although acid itself has no effect on the pancreas

Secretin, a polypeptide has been isolated and crystallized in pure form

There is some difference in the type of fluid secreted when the pancreas is stimulated by way of the vagus nerves or when stimulated by the hormone secretin With nervous stimulation, the secretion of the pancreas is rich in enzymes but is rather thick in consistency and small in volume The cells can be exhausted of their zymogen granules by continued vagal stimulation

The hormone, upon stimulating the pancreas brings about the production of a watery fluid high in alkali (bicarbonate) concentration but with a very small quantity of enzymes This thin watery fluid aids in cleaning the crevices between the villi and making the chyme more watery in order to favor more rapid absorption through the walls of the intestine and more rapid flow through the lumen

INTESTINAL JUICE (SUCCUS ENTERICUS) AND ITS ACTION

The whole surface of the small intestine is covered with finger like projections called *villi* In man 18 to 40 villi are present in each square millimeter of intestinal surface there being about 5 000 000 altogether

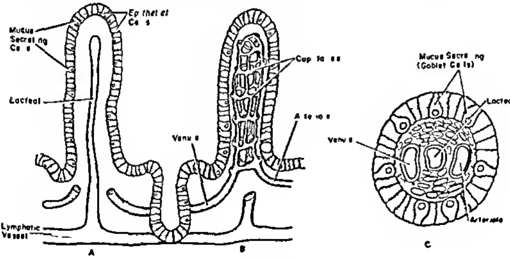


FIGURE 275

The villi of the intestinal tract A villus with central lacteal (blood vessels removed) B villus showing blood vessels (lacteal removed) C cross section taken near base of villus

Their structure is shown in Figure 275 They are richly supplied with capillaries through which digested food materials are absorbed, at the center of each is a lacteal, into which most of the fat is absorbed The villi function in absorption and in presenting an enormous surface for that absorption

Secreting cells on the surface and at the base of the villi are discussed elsewhere

About 3000 cc of intestinal juice is produced per day, consisting of about 98 per cent water and 2 per cent solids Sodium carbonate and bicarbonate are abundant, giving to the secretion an alkaline reaction, between pH 7 0 and 8 5 The intestinal juice contains several enzymes

The Enzymes of the Intestinal Juice

One of the enzymes produced in the walls of the intestine, *enterokinase*, mentioned previously, activates trypsinogen of the pancreatic juice to trypsin

Also present are enzymes that hydrolyze the disaccharide sugars to monosaccharides These enzymes are *sucrase* or *invertase*, *maltase* and *lactase*, which act upon sucrose, maltose and lactose, respectively One molecule of sucrose breaks down to one molecule of glucose and one of fructose, maltose, to two molecules of glucose, and lactose, to one molecule of glucose and one of galactose

The intestinal juice has been known for some time to contain materials acting not upon native protein, but upon peptides—the products of partial protein digestion At first, that portion of the intestinal juice having a peptidase activity was called *erepsin* More recently, however, specific components have been identified and so the name erepsin is no longer in use *Aminopeptidase* acts in a manner similar to carboxypeptidase, except that it splits off amino acids from the polypeptide chain having their amino ($-NH_2$) group free *Dipeptidases* are also present and act upon compounds made up of two amino acids They are quite specific, that is each one may act only upon a combination of particular amino acids

The intestinal juice contains also small amounts of *lipase*, which is, nevertheless, of considerable importance It has been shown that fat digestion may occur even though the pancreas has been removed, or its duct ligated

Control of Intestinal Secretion

The contact of food with the walls of the intestines is one of the best means of stimulating intestinal gland secretion Stretching the walls of

Bile

The digestive function of the liver is apparent chiefly in the action of certain constituents of bile About 400 to 800 cc of bile is produced daily by the liver cells it is a yellow to dark brown solution consisting of 98 per cent water and 2 per cent solids Its important constituents from the standpoint of digestion are the bile salts—*sodium glycocholate* and *sodium taurocholate* These salts are responsible for the emulsification of fats and lipoids in order that they may be digested by the enzyme lipase of the pancreatic juice and then absorbed This action breaks down the fats into *glycerol* and *fatty acids*

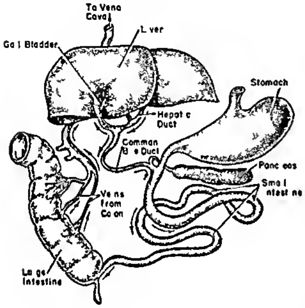


FIGURE 277

The relationship between the liver gall bladder and intestine and the flow of the bile The arrows indicate the flow of bile salts from the liver where they are produced to the gall bladder and thence to the duodenum Most of the bile salts are reabsorbed by the capillaries of the large intestine and are carried back to the liver for further use

No enzymes are present in bile it is alkaline in reaction (*p*H 7 5) and contains besides the substances already named fatty acids lecithin cholesterol inorganic salts and the bile pigments *bilirubin* and *biliverdin* Bilirubin is a brownish colored pigment produced as a breakdown product of hemoglobin in the livers of carnivorous animals It is heme minus its iron Biliverdin oxidized bilirubin is a yellow to greenish pigment produced in the livers of herbivorous animals

When stimulated nerve fibers leading to the liver by way of the vagi increase bile production If the blood supply to the liver is increased bile flow is increased and vice versa However the nature of the regulation of bile formation is not entirely clear

THE GALL BLADDER

The function of the gall bladder is storage of the bile, secreted by the liver cells at all times. If this bile were carried directly to the intestine, much of it would be wasted, since it is useful only after food containing fats or lipoids has entered the intestine. For this reason, it is advantageous to store it until needed. The bile flows to the gall bladder by way of the *hepatic duct* and the *cystic duct* which leads directly into the gall bladder. The *common bile duct* is formed by the union of these two and leads to the intestine, entering it along with the pancreatic duct. At its end near the intestine is a sphincter muscle which is usually closed, damming the bile back into the gall bladder.

The gall bladder is a baglike reservoir, storing bile temporarily. It holds about 40 to 50 cc. of fluid, gradually becoming concentrated by the reabsorption of water and alkali into the blood stream

The gall bladder contracts from time to time, forcing its contents into the intestine. This contraction is brought about by nervous action. The smell or taste of food initiates the reflex, causing the gall bladder to contract slowly and the sphincter to relax at the same time. A hormonal control also exists and is effective even after the nerves leading to the gall bladder are cut. A hormone, *cholecystokinin*, produced in the intestinal mucosa by the action of fatty foods, is absorbed into the blood stream and carried to the gall bladder which it stimulates to contraction.

Jaundice or Icterus

When an excessive amount of bile pigment is present in the blood stream, it diffuses into the tissues, imparting a yellow color to them This is called *jaundice* or *icterus*, three types of which are known:

1. *Hemolytic jaundice* is caused by an overproduction of bile pigment due to increased red cell destruction.

2. *Obstructive jaundice* is caused by blockage of the hepatic or common bile ducts. This blockage may be caused by (a) gallstones formed from cholesterol or calcium, or from a combination of the two, or to a parasitic obstruction of the duct, (b) a tumor compressing the duct, or (c) congenital closure.

3. *Toxic* or *infective jaundice* as a result of liver damage, is caused by the failure of the liver to excrete its bile pigments because of a toxic or poisonous action such as that of arsenicals, or because of infection.

SECRETIONS AND ACTION OF THE LARGE INTESTINE

No enzymes are secreted by the large intestine or by any organs connected with it, although mucus is secreted in great quantities, aiding in lubricating and softening the fecal matter There is very little need for enzyme secretion since the chyme, by the time it reaches the large intestine, consists chiefly of undigestible material and large quantities of water

In herbivorous animals some digestion of cellulose takes place in the large intestine, this, however, is carried on by bacteria, producing enzymes that hydrolyze cellulose

Before it passes out of the body, the fecal matter of the large intestine usually loses most of its water Feces contain large quantities of mucus, bacteria, epithelial cells, undigested waste materials, and excretions, such as salts and heavy metals

Constipation, or inability to defecate, results from stagnation in the descending colon because of too great a water absorption or too long a retention Many factors, such as improper diet, abusive use of cathartics, failure to eliminate when ready, and a spastic colon, contribute to constipation

The headache and general ill feeling appearing along with constipation may be caused chiefly by the absorption of such toxic substances as *indole*, *skatole*, and *phenols* from the large intestine These are products of intestinal putrefaction, normally not produced in any great quantity and hence not absorbed unless the feces remain in the colon too long

ABSORPTION FROM THE ALIMENTARY CANAL

The amount of absorption from the mouth, pharynx, and esophagus can be regarded as nil The same can be said for the stomach except for *alcohol* About 30 to 40 per cent of the alcohol taken into the stomach is absorbed there, the remainder being absorbed from the small intestine This is one reason for its sudden action when it is imbibed on an empty stomach However, its absorption in the stomach depends upon many factors

Practically all the digested food material is absorbed through the wall of the small intestine This includes the *simple sugars, amino acids, fatty acids*, and *glycerol*

The absorption of some of these materials is carried out by simple diffusion or dialysis, as in the case of water, salts and amino acids However, some absorption is of a selective nature requiring a greater amount of oxygen, glucose, galactose, and fats are absorbed in this manner

Most of the fat (about 60 per cent of it) is absorbed into the lacteals

of the villi and from there carried via the lymphatics to the thoracic duct, which empties it into the blood stream of the veins in the neck region The other food products are absorbed directly into the capillaries of the villi

Water is chiefly absorbed in the colon although some of it is absorbed in the small intestine Salts and gases are also absorbed in the colon

ADDITIONAL READING

Babkin, B P, *Secretory Mechanism of the Digestive Glands* (New York Hoeber, 1950) A detailed account of structure, function and control of glands of digestion

Hawk, P B, B L Oser and W H Summerson *Practical Physiological Chemistry*, 12th ed (Blakiston 1947) chs 13–19 Biochemistry of digestion

Thomas, J E, *The External Secretion of the Pancreas* (Springfield Charles C Thomas 1950) Reports on studies of pancreatic enzymes, their functions and factors controlling their secretion

the inefficiency of the energy utilization of protoplasm The living organism is said to be 25 to 30 per cent efficient, which is high compared with the efficiency of physical machines—70 to 75 per cent of the energy being lost by the organism in the form of heat Some of the heat produced in this manner is utilized by higher animals—mammals and birds—in maintaining a constant, fairly high temperature in their bodies However, considerable quantities of energy are lost as heat even in these animals for much more is produced than is needed

2 *In the form of work* Muscle cells utilize by far the greatest amount of energy for work, although secretory or gland cells also carry on much ' work To a lesser extent all body cells do some work and therefore, need energy for it

3 *In the form of stored energy* Energy may be stored in the form of glycogen or fat to be used at a later date That energy stored up in the formation of new protoplasm, whether for growth or tissue repair must also be included under the term, stored energy

THE CALORIE

The unit of heat employed in physics is the *calorie* which is defined as the amount of heat required to raise 1 g of pure water from 15 degrees C to 16 degrees C In metabolism studies, the unit used is the large calorie (C), actually 1000 times this, or a kilocalorie (Kcal), the amount of heat required to raise 1000 g of water 1 degree C

The calorific value of foods can be measured experimentally by two methods One is by measuring the total heat of combustion produced by a food of known weight, this is done in a bomb calorimeter The other method calculates the heat production value by determining the amount of oxygen needed for complete combustion

By these methods it has been found that when completely oxidized, 1 g of carbohydrate yields about 4 Calories, 1 g of fat, about 9 2, and 1 g of protein, about 5.4 Calories Actually because of incomplete combustion of this food, only 4 3 Calories are produced in the body from 1 g of protein

The amount of oxygen required by foods varies for each because of the different amounts of oxygen in their molecules For complete combustion carbohydrates require about 0 8 liters of oxygen per gram fats, about 2 0 liters, and proteins 1 6 liters

If we consider caloric production on the basis of oxygen consumed we find that for every liter of oxygen, approximately 5 Calories of heat energy are produced For carbohydrates it is only slightly more than 5 and for fats and proteins, slightly less than 5 Calories

36

Metabolism

GENERAL METABOLISM

METABOLISM is usually defined as the sum total of all the chemical processes that occur in the body of an organism

Metabolism includes both constructive and destructive processes The term *anabolism* is used for the constructive type including all of the synthetic processes of the body, such as formation of protoplasm, starch, fat, enzymes, and hormones, and production of immune bodies For the destructive processes we use the term *catabolism* which includes such processes as oxidation and hydrolysis, resulting in the production of energy

Special metabolism may be concerned with specific types of foods, such as *protein metabolism*, or a particular organ, such as *liver metabolism*, or with a tissue, such as *nerve* or *muscle metabolism*, or a cell, such as *cell metabolism*, or in the case of gaseous exchange and utilization, we may speak of *respiratory metabolism* These are subdivisions of general metabolism

METABOLISM OF FOODS

Because the energy needed for maintenance of life growth and bodily functions, is obtained from the foods we eat, the metabolism of foods is of utmost importance Since the greater part of our food is carbohydrate, and, since about 60 per cent of the proteins and 10 per cent of the fats ingested may be changed to carbohydrate, carbohydrate is obviously the most important of all foods for production of energy Foods must eventually be obtained from plants since the plant can utilize the radiant energy of sunlight in producing its own food material Animals cannot do this, and consequently, are entirely dependent upon foods that have been synthesized by other organisms

Disposal of Energy

The energy produced by various foods is disposed of in three ways

1 *In the form of heat* The law of conservation of energy holds true for the living organism as for any chemical or physical reaction that is, the energy intake and outgo are equal although much of the outgo is wasted by

the inefficiency of the energy utilization of protoplasm The living organism is said to be 25 to 30 per cent efficient, which is high compared with the efficiency of physical machines—70 to 75 per cent of the energy being lost by the organism in the form of heat Some of the heat produced in this manner is utilized by higher animals—mammals and birds—in maintaining a constant, fairly high temperature in their bodies However, considerable quantities of energy are lost as heat even in these animals, for much more is produced than is needed

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If we consider calorie production on the basis of oxygen consumed we find that for every liter of oxygen approximately 5 Calories of heat energy are produced For carbohydrates it is only slightly more than 5, and for fats and proteins, slightly less than 5 Calories

By knowing the respiratory quotient and the figures presented above it is possible to gain some information concerning the type of metabolic processes occurring in animals

DETERMINATION OF METABOLISM

There are two methods by which metabolism can be ascertained The one is the *direct method* in which special chambers are built so that the heat water and CO produced or the O and foods utilized by the body of an animal or man can be accurately determined over a known period of time This is known as *direct calorimetry*

The *indirect method* depends on the fact that practically all of the heat produced in living organisms is the result of oxidations Therefore if the *oxygen consumption is known it is possible to estimate the heat production*

BASAL METABOLIC RATE (B M R)

Basal metabolism is the metabolism existing when an animal or plant is at complete rest It consists of the minimum amount of metabolic activity necessary to continue the living state of an organism Actually this condition is never obtained in animals but in the case of humans standard conditions have been set up which must be followed strictly in order to come as nearly as possible to this basal state

A diagram of the apparatus used for determining B M R is illustrated in Figure 278 The subject goes without food for at least twelve hours before testing because of the rapid and definite increase in oxidation when food is ingested He is placed in a reclining position for at least a half hour having avoided physical exertion en route to the laboratory Pure oxygen is placed in the bell of the B M R outfit The nostrils are clamped so that the respired air passes in and out through the mouthpiece only The valves determine the direction of movement of the air that expired always passes through the soda lime or other absorbent in the tank so that CO is removed In this way the oxygen consumed can be noted The bell gradually lowers in the tank as the oxygen is removed and by recording the gradual change during a six to eight minute period on a moving kymograph drum as illustrated we can compare the condition of the subject with that of normal standards

EFFECTS OF VARIOUS FACTORS ON BASAL METABOLISM

Several factors affect basal metabolism variously One might suppose that an ideal condition for basal rate would be during sleep However depth of sleep is difficult to ascertain or to regulate Dreaming and bodily

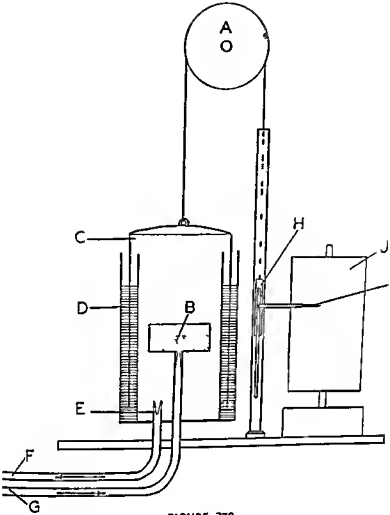


FIGURE 278

Diagram of the apparatus used in ascertaining basal metabolism A pulley B container with soda lime for absorbing carbon dioxide C bell containing oxygen which moves up and down in the water jacket D as air enters or leaves E exit valve which prevents air from passing back into the bell after it leaves F exit tube leading to the mouthpiece G inlet tube leading from the mouth to the soda lime container (another valve just below the container prevents air from backing up into this tube) H counter balance J kymograph drum K writing point attached to the weight to record the movements of the bell (From Pace and Riedesel *Laboratory Manual for Vertebrate Physiology*)

movements might cause increase in metabolism depending upon the type of dream, or the extent of movement

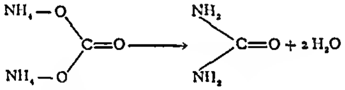
Age is also a factor, the B M R increasing during early childhood up to about five to eight years and then decreasing as one ages *Sex* is a factor the rate is 5 to 10 per cent lower in females than in males

The pathological conditions of fever and *hyperthyroidism* are associated with an increase whereas *hypothyroidism* and *deficiency* in *pituitary* and *adrenal cortex function* are associated with a decrease in B M R

Excitement, *food* and *exercise* increase metabolism, *starvation* and *sleep* lower it All of these factors must be considered in any measurement Often the figures obtained for a particular person may be of aid in diagnosing a pathological condition

PROTEIN METABOLISM

Protein metabolism is essential for growth and body maintenance Proteins are the most complex substances known being formed by the union of many amino acids During the digestive processes, they are hydrolyzed to amino acids These are absorbed into the capillaries combining to form the venules leading to the portal vein, which enters the liver About 30 per cent of the amino acids are destroyed by the action of the liver cells which *deaminize them* This means simply that the amino ($-NH_2$) group is detached from the molecule and unites with carbonic acid to form ammonium carbonate The ammonium ion is very toxic to most living cells because it can penetrate rapidly through living membranes Ammonium salts are consequently, detoxified by the liver cells which can change them to urea



Ammonium carbonate Urea

Urea produced in this way, that is directly from the absorbed amino acids is called *exogenous* urea That produced within the cells as a product of metabolism is *endogenous* Both types are carried to the kidney where most of the urea is excreted Because of the action of the liver cells on amino acids rather large quantities of protein are necessary in the diets of animals The amino acids that escape the liver are carried to the tissues where they are needed to build up proteins and protoplasm

That part of the amino acid molecule remaining after deamination may be converted to glucose or glycogen in the liver, or it may be oxidized to carbon dioxide and water

In muscle large quantities of *creatinine* are produced being derived from

creatine which is of great importance in muscle metabolism The concentration of creatinine in the urine is generally a good indication of the activity of the muscles

Proteins are the main food materials of the diet that serve as a source of nitrogen Therefore one can estimate the degree of protein metabolism by analyzing the urine and other excreta for nitrogen In normal adults the nitrogen intake should equal the nitrogen output this being called *nitrogen balance* Sometimes conditions are such that the nitrogen excretion is greater than the intake resulting in *negative nitrogen balance* found during starvation fever and in diets low in protein or containing proteins deficient in *essential amino acids* which have already been listed (page 435) Essential amino acids must be present in the food of the diet since they cannot be synthesized by the body tissues We speak also of *nonessential* amino acids however these are nonessential only in relation to the diet for they are needed by the tissue but may be synthesized in the body from essential amino acids Corn for example is deficient in lysine tryptophane and methionine gelatin in lysine and tryptophane The body cannot synthesize these amino acids and therefore growth or even maintenance of an animal is impossible if it obtains only these proteins

At times the nitrogen intake exceeds the output and this condition is termed *positive nitrogen balance* This is evident in young animals from the time of conception to the adult—that is during the growing stage when nitrogen is utilized in building up proteins and protoplasm It occurs also during convalescence and recovery from starvation

Theoretically, 20 to 25 g of protein are needed by the normal adult per day to make up for the protein loss due to normal wear and tear However this minimum quantity is not dependable and as a safety measure larger quantities should be and usually are ingested

Uric acid is another nitrogenous waste product of protein metabolism derived from the so-called *purine bases* constituting a part of the molecule of *nucleoproteins* These proteins are constituents of cells especially cell nuclei Sometimes because of faulty kidney excretion uric acid which is only slightly soluble is deposited in the joints resulting in the condition called gout'

CARBOHYDRATE METABOLISM

The carbohydrates as *monosaccharides* are absorbed from the intestines into the blood of the portal system Glucose galactose and fructose are said to be absorbed *selectively* and not according to their diffusion rates This is probably accomplished by a phosphorylation process (union of

glucose with phosphorus) taking place at the point of absorption after which the free sugars are carried by portal circulation to the liver where most of the glucose is removed and stored as glycogen The removal from the blood is also accomplished by means of phosphorylation in which glucose phosphate is formed and acted upon by enzymes combining several glucose molecules to form glycogen The process is known as *glycogenesis* The other monosaccharides must first be changed to glucose in the liver and then glycogen may be formed Some of the glucose however is transformed into fat and stored in the fat depots of the body

The quantity of glycogen in the liver varies from time to time and in different individuals but on the average is around 5 to 7 per cent of the weight of the liver and often may be as much as 10 per cent Some glycogen is found in muscles and may average 1 per cent of the muscle weight

There is always some glucose in the blood stream The normal average value is 90 to 100 mg per 100 cc of blood and at any time that it tends to decrease the liver is called upon and gives up some of its glucose by the reverse process of glycogenesis called *glycolysis* In muscle glycolysis does not result in the formation of free glucose but instead the glucose phosphate formed is broken down anaerobically to furnish lactic acid with the resultant liberation of energy

After a heavy carbohydrate meal the glucose concentration of the blood may become somewhat greater than normal This occurs when such large quantities are absorbed that the liver is unable to store it The threshold for blood sugar is 150 to 180 mg per 100 cc of blood any sugar above this amount will show up in the urine the condition being called *glycosuria* The specific type cited above is known as *alimentary glycosuria* and is only temporary The general topic of glycosuria will be treated under excretion (Chapter 37)

Carbohydrates as we have already learned are the chief source of body energy The final end products are carbon dioxide excreted chiefly by way of the lungs and water which may be used by the body or excreted by various routes

FAT METABOLISM

Neutral fats (or true fats) are metabolized to their basic constituents fatty acids and glycerol (page 437) chiefly by the lipase of the pancreatic juice this process is aided by the presence of bile salts which have an emulsifying action on fats and also aid in the absorption of the end products

The end products unite again to form neutral fat as soon as they get into

the lining cells of the villi and are then taken into the lacteal, at least 60 per cent is absorbed in this way

The neutral fats are stored in special localities within the body, called *fat depots* The greatest storage space of this type in the body is just beneath the skin although comparatively large amounts are deposited in the omentum, the pericardium, the area surrounding the kidneys and adrenals, and also that surrounding the striated muscle fibers The *omentum* is that part of the peritoneum connecting the stomach with the liver and transverse colon It hangs down in front like an apron and owing to fatty deposition, is mainly responsible for the increase in size of the abdominal region

The neutral fats stored in animal tissues tend to be constant for each species This means that stored fat of one species if ingested by a second soon assumes the characteristics common to the fat of the second type However, some resemblance exists between the lipoid substances found in protoplasm of all species

Some of the *phospholipids,* or fats combined with phosphoric acid are extremely important to the normal functioning of protoplasm These consist of lecithin, cephalin, and sphingomyelin They are particularly important in cell membranes as an aid in regulating their permeability The true fats are ultimately oxidized to carbon dioxide and water, this oxidation occurring in any cell containing the proper enzymes

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Fulton, J F *Textbook of Physiology,* 16th ed (Saunders 1950), chs 51, 52 Metabolism of foods measurement of metabolism

37

Physiology of Excretion

NEED FOR EXCRETION

IN ALL CHEMICAL PROCESSES that occur in the animal body waste products or by products are produced for which there is no immediate need In fact they may be poisonous and must be eliminated

Plants do not usually have special organs for getting rid of waste materials They merely store them in the cell walls or within the cells themselves However, some of the lower plants living in water, can rid themselves of their wastes by diffusion Animals, for the most part, have special structures for elimination

The so called excretory organs" of animals appear to have a second function aside from that of the removal of waste products They are also specialized as *osmoregulators* (the elimination of excess water) Usually relatively great quantities of water are ingested with the food of animals This must be removed, otherwise there would be danger of the tissues becoming waterlogged

MATERIALS EXCRETED BY ANIMALS

1 *Water* As pointed out above, most animals including land, sea, or fresh water types, take in large quantities of water Some of this water may be utilized by the body cells, but most of it is eliminated by the excretory organs That this water, which merely passes through the body, should be referred to as an excretion, is questionable It plays no part in metabolism of the cell and is not, therefore, one of its excretory products On the other hand, water formed within living cells during normal metabolic activities is called metabolic water and is a true excretion Since both types pass out of the animal system by way of the same structures, it is impossible to differentiate between them

2 *Carbon dioxide* Excretion of carbon dioxide takes place by way of the lungs This process has already been covered in the discussion on respiration (page 375) A small amount of carbon dioxide becomes a part of the urea molecule and is excreted as such, as well as in the form of calcium carbonate

3 *Nitrogenous compounds* Usually when we speak of excretion, we are

referring to kidney excretion, the excretory substances of which are for the most part nitrogenous. The nitrogenous excretions of vertebrates is fairly well known but that of many invertebrates is still not very clearly understood. It has been shown that in some invertebrate forms, such as the annelid worms, mollusks, and crustaceans, the excretory processes and substances are fundamentally similar to those of the vertebrates.

Urea and uric acid are two of the most important nitrogenous compounds excreted by animals, although ammonia, hippuric acid, and creatinine also may appear in urine.

During normal metabolism, urea is produced. Urea in the excretions of vertebrate animals may be of two types, exogenous and endogenous. Actually, most of the urea produced in the body is formed in the liver, other tissues producing very little. However, in either case, the urea formed is a true waste product, although most of it is formed by a very special metabolic process in a comparatively small portion of the body.

In the intestines, considerable quantities of ammonia are produced by putrefaction. This product is absorbed through the intestinal wall and carried by the portal system to the liver where it is detoxified—changed to urea by the liver cells. This also, is exogenous urea.

The liver of vertebrates is an excretory organ. The urea it forms must pass, by way of the circulatory system, to the kidneys to be excreted. The liver also excretes directly into the intestines. *Bilirubin*, *biliverdin*, and other wastes pass into the intestinal tract by way of the bile duct.

Urea and uric acid appear to be eliminated in greatest concentration by terrestrial animals, whereas ammonia and amino acids are the waste products most eliminated by aquatic forms. Urea is the chief nitrogenous excretory substance of fish, amphibia and mammals, whereas uric acid is the primary excretory product of reptiles and birds.

The environment of the animal apparently plays an interesting role in determining the nature of the nitrogenous excretory products. Since ammonia is extremely soluble in water, and since it can be released rapidly and diffuses into the environment, it serves well as an excretory product for aquatic forms. The same would hold true, to a slightly lesser extent, for urea, since it also is quite soluble in water. Uric acid, on the other hand, because of its relative insolubility in water, is excreted in many cases in the crystalline form, the 'urine' being accompanied by very little water. Uric acid is the main excretory product of many animals which are adapted to an arid terrestrial life, for example, reptiles—snakes and lizards, thus water conservation is effected.

4. *Nonnitrogenous compounds.* Nonnitrogenous substances also are ex

creted, many of them appearing only as temporary excretory materials. Many inorganic salts appear in the urine and other excretions. Chief among them are sodium, potassium, calcium and magnesium chloride, sulfate, or phosphate.

EXCRETION IN INVERTEBRATES

Protozoa. The nitrogenous waste products of protozoan organisms are as variable as the wastes of vertebrates. In some, urea is excreted, in others uric acid, and in others ammonia. It is not always known just how these products are excreted by different species. They are found only when the solution in which the various protozoan cells have been living, is analyzed. So far, attempts to show that the contractile vacuole of *Paramecium* contains nitrogenous wastes have failed although we are inclined to think of it as an excretory organ. It does function as an osmoregulator, an essential in fresh water. In many, if not all, protozoan species, the nitrogenous and other

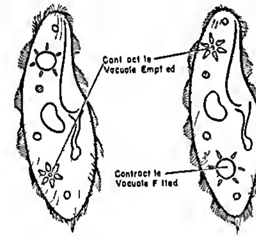


FIGURE 279

Paramecium showing manner in which the contractile vacuoles function in osmoregulation.

wastes could diffuse through the cell membrane to the outside. Urea and ammonia pass through cell membranes rapidly, hence, contractile vacuole would be unnecessary for the excretion of these substances. At any rate, there is a much higher concentration of these products in the surrounding liquid environment than can be accounted for by way of the contractile vacuole indicating that excretion is carried out by diffusion of waste products directly through the cell membrane. Many marine forms do not have contractile vacuoles or comparable structures and the only possible means for excretion is by diffusion through the cell membranes. Evidently, therefore, the contractile vacuole is chiefly an osmoregulator and not an excretory organ.

Porifera and Coelenterata There are no specialized excretory organs in the porifera or coelenterates Some investigators claim to have found uric acid in one species of sea anemone but, in most cases, ammonia and to a lesser extent, urea, appears to be the primary nitrogenous waste material

Platyhelminthes and Nemathelminthes In the Platyhelminthes or flat worms, a very interesting flame cell excretory system is found (Figure 35 page 52) This is sometimes referred to as a *protonephridium* because it is thought that the *nephridia* of annelid worms developed from them These cells are quite numerous and appear as branches from the two main excretory tubes which empty their contents by way of excretory pores They are thought to be osmoregulatory in function nothing is known concerning the waste products excreted

In Nematodes the excretory structures are very similar to those of the flatworms

Annelida The earthworm a typical member of this group has well developed *nephridia* one pair in each segment (Figure 280) These are the excretory organs although there may be other excretory structures such as the amoeboid cells that collect waste materials and then travel to the body surface to be thrown out Glandlike structures occurring also along the nephridial tube are thought by some to excrete substances into it These nephridia are well supplied with blood vessels There is still much to be discovered concerning excretion and excretory systems of annelids

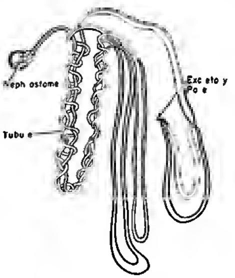


FIGURE 280

Nephridium of earthworm

Echinodermata The echinoderms have no well defined excretory system but some loss of nitrogenous wastes takes place through the water vascular system In starfish amoeboid cells take up waste materials in all parts of the body, carry them to the respiratory papillae on the surface and are then expelled Urea and ammonia are found in low concentration in the water vascular system of the echinoderms

Arthropoda The green glands of crustaceans which are found at the base of each antenna are evidently the chief organs of excretion In addi

tion, they act as osmoregulators in fresh water species The liver of crustaceans is also an important excretory organ in that it can extract foreign materials, especially uric acid or urates from the blood stream and pass them out by way of the intestines

Uric acid is the normal nitrogenous excretion of insects, although urea, ammonia and amino compounds are also excreted by some species The *Malpighian tubules* are the structures concerned with excretion, their numbers varying with different species Both urates and carbon dioxide are eliminated through them

Many granules and crystals occur in the cytoplasm of the cells surrounding these Malpighian tubules most of the crystals being uric acid This is excreted from the cell in the upper part of the tubules in the form of soluble urates, but is precipitated again in the form of uric acid because of the absorption of water and base in the lower part of the tube A somewhat similar mechanism is found in birds and is a means of conserving water The type of respiration employed in insects results in the loss of much water, hence, any means for conserving it elsewhere is beneficial to the insect The excretion of nitrogenous waste products in the form of uric acid rather than urea, is such a means

UTILIZATION OF EXCRETORY PRODUCTS

Excretory products are sometimes utilized by animals for various purposes Many of the *Protozoa* form shells that may be made of calcium carbonate, silica or nitrogenous materials The *Porifera* form both siliceous and chitinous skeletal structures and the corals of the phylum *Coelenterata* have well known skeletons made of calcium carbonate all of which are undoubtedly waste materials The exoskeleton of the insects consists of *chitin*, this is a nitrogenous excretory product (page 37) Uric acid is a waste material but is used by certain butterflies to give the pure white markings on their wings Calcium carbonate is used in the formation of shells in oysters and clams The materials that make up the bones, hair, and nails of vertebrates were waste products in animals that existed before vertebrates were developed

EXCRETION IN MAMMALS

Waste products are excreted by the mammal through the *lungs, skin, alimentary canal,* and *kidneys* The liver can also be regarded as an excretory organ, since it excretes various substances by way of the bile Carbon dioxide and water leave the body through the lungs, water and traces of nitrogenous wastes via the sweat glands of the skin, undigested and un

absorbed wastes, by way of the alimentary tract and the anus, and both endogenous and exogenous excreta other than gases, through the kidneys.

THE MAMMALIAN KIDNEY IN RELATION TO THE URINARY SYSTEM

Gross Structure

The importance of the mammalian kidney is evident by the quantity of oxygen it consumes. The consumption of oxygen by a tissue is proportional to the tissue's activity. The kidneys expend considerable energy in performing their work. They represent only about one half of one per cent of the total body weight but utilize about nine per cent of the oxygen taken in. A large part of the kidney consists of "reserve tissue", in other words, only a part of the kidney tissue functions at any given time, the remainder being held in "reserve." It is for this reason that a person can live with only one kidney.

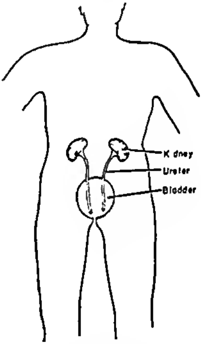


FIGURE 281

Relative positions and sizes of kidneys, ureters, and urinary bladder in the human body.

Fishes and amphibians possess a *mesonephros*, an excretory and osmoregulatory organ in which tiny tubules collect fluids directly from the body cavity and also receive materials filtering from an adjacent blood capillary. However, the mammalian kidney is by far the best known of the special excretory structures. It may be referred to as a *metanephros* and fundamentally is built on the same general plan as is the mesonephros, except that all wastes come from the blood stream. Figure 281 illustrates grossly the important parts of the mammalian urinary system including the *kidneys*. Two tubes, the *ureters*, connect the *hilus* of the kidney with the *urinary bladder*. The urine is stored in the bladder which from time to time is stimulated to contract so as to void the fluid by way of the *urethra* which carries it to the outside.

Microscopic Structure

The important functional units of the kidney are the *nephrons*, located in its cortical portion. Each nephron consists of a *Malpighian body* (or

renal corpuscle) and a *renal tubule* which leads away from the Malpighian body to a collecting tubule. About one to one and a half million of these units are present in each kidney, however, they do not all function at the same time.

The Malpighian Body or Renal Corpuscle. Each Malpighian body measures approximately 200 microns in diameter and is made up of two parts: the *glomerulus* which is a tuft of capillaries that fits into *Bowman's capsule*. In its evolution from lower forms the Malpighian body was probably developed by an invagination of the expanded end of a nephridial tubule into which the nearby capillaries passed. The cells of the walls of the capsule surrounding the capillaries are very thin, as are the capillary walls. Thus, the excretory contents of the blood in the capillaries can readily pass through the porous walls into the capsular cavity. The capsular wall next to the glomerulus is called the *visceral layer*, that to the outside, the *parietal layer*.

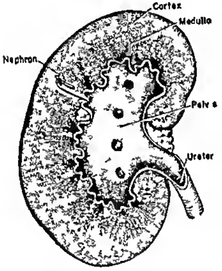


FIGURE 282

Section through kidney to show position of nephrons

The Renal Tubule. Actually Bowman's capsule is part of the renal tubule, but because of its close association with the glomerulus it is usually included with it. The renal tubule has three distinct segments. The first of these is the *proximal convoluted tubule* which leads directly from Bowman's capsule, is about 55 microns in diameter and 14 mm. in length. Following the proximal tubule is *Henle's loop* about half of which is very thin walled. It is about 16 mm. long and consists of a descending limb, the loop itself, and an ascending limb. Most of this structure lies within the renal medulla.

The *distal convoluted tubule* is a continuation of the ascending limb of Henle and is similar to the proximal tubule. It is about 5 to 6 mm. long and leads into the collecting tubule.

Thus the length of a single nephron is about 1¼ to 1½ in. and it has been estimated that if all these units of both kidneys were placed end to end they would stretch over a distance of 30 to 45 miles.

The excretory function of the nephron ends at the collecting tube, which is merely a passageway for the urine. The smaller collecting tubes unite

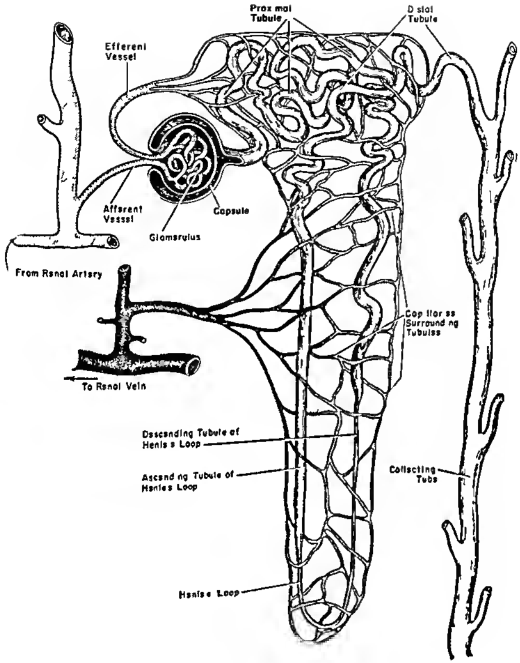


FIGURE 233

Microscopic view of the nephron and its constituent parts

der. Its constituents and their approximate concentrations are given in Table 18.

TABLE 18

The Composition of Human Urine

Substance	*Daily Output (in grams)*
Water	1200 to 1500
Urea	30.0
Uric acid	0.5
Creatinine	1.0
Hippuric acid	1.0
Sodium chloride	15.0
Sulfuric acid	2.5
Phosphoric acid	2.5
Ammonia	0.7
Potassium	3.3
Magnesium	0.5
Calcium	0.3

In all, about 60 g. of dissolved substances are excreted daily in the urine. This varies from day to day and in different individuals. For example, the creatinine content is much greater during laborious muscular work than during mental work, the creatinine being a waste product of muscle metabolism.

The reaction of the urine is usually acid but this varies greatly. On a normal mixed diet it usually has a hydrogen ion concentration of pH 6.0. On a protein diet an acid urine is produced, whereas a carbohydrate diet produces an alkaline reaction. Thus the body has a means by which to rid itself of excess acids or alkalies.

FUNCTIONS OF THE MAMMALIAN KIDNEY

The general functions of the mammalian kidney have already been mentioned, but can be summarized here. The kidney serves (1) as an *osmoregulator* by excreting excess salts and excreting and reabsorbing water; (2) as an excretory organ for certain threshold substances when they become too concentrated in the blood stream, (3) as a means of excreting foreign materials of no value to the body (since they are not threshold substances they are not reabsorbed in the tubules and are excreted entirely), (4) as a regulator of acid base equilibrium by excreting excess acid or base from the blood.

GLOMERULAR FILTRATION

The first stage of urine formation occurs in the Malpighian body where because of the high pressure of the blood within the glomerular capillaries a great deal of *filtration* takes place The arrangement of the capillaries in the Malpighian body is an ideal one The *afferent arteriole* as it enters the corpuscle loses its muscular coat and divides into about fifty capillary loops thus furnishing a large surface to the blood so that relatively large *quantities of water and dissolved substances* can pass through the thin membranes easily These capillaries collect again to form the *efferent arteriole* which is only about one half the diameter of the afferent its area is therefore only about one fourth of the latter These arterioles are very important in regulation of blood flow through the glomeruli By constriction they can decrease the flow or by dilation increase it

EFFECTIVE PRESSURE IN RENAL CORPUSCLE

The energy for filtration is that carried to the capillary from the ventricular contraction This is true for all capillary filtration in the body The difference between renal and other body capillaries is the degree of force exerted against their walls by the blood stream For most capillaries the blood pressure is between 25 and 30 mm Hg but the capillaries of the kidney because of the almost direct route from the aorta must withstand a blood pressure of 75 mm Hg It is found that the substances that filter through the renal capillaries are not always the same as in others For example normally there is no protein filtration in the kidney although this occurs for proteins of small molecular diameter through capillaries elsewhere in the body Only water and molecules of less than 70 000 molecular weight pass through the renal capillaries

The force of hydrostatic pressure of the blood stream is counteracted by smaller forces or pressures on the capsular side of the membrane These are (1) *osmotic pressure* of the plasma proteins (especially after losing water by filtration) which is equal to approximately 30 mm Hg and (2) the *pressure which accumulates in the tubule* and forces the capsular fluid down the tubule toward the collecting duct this is not very great but varies between 10 and 20 mm Hg

Thus the 75 mm pressure of the blood which forces water and its dissolved substances into the capsule is counteracted by opposite forces equal to 40 or 50 mm Hg that tend to prevent the passage However since there is still an effective pressure of 25 to 30 mm., glomerular filtration takes

place at a relatively rapid rate These forces are illustrated in Figure 285

The volume of glomerular filtrate depends upon the rapidity of blood flow and its pressure through the glomerular capillaries The total volume of the filtrate depends upon this as well as upon the number of active glomeruli These can be regulated by constriction or dilation of the arterioles

About 20 per cent of the blood that leaves the heart per unit time passes through the renal artery Since there are about 5 liters of blood in the average adult body (3 liters of plasma) and since this amount passes through the heart every minute, the total blood volume will pass through the renal vessels every 5 min In other words 1000 to 1200 cc of blood flows through the glomerular capillaries every minute and from this approximately 125 cc of glomerular filtrate is formed No proteins are found in the glomerular filtrate but it contains all the other water soluble constituents of the plasma in the same concentrations as they occur in the plasma

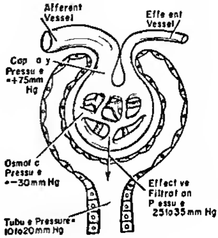


FIGURE 285

Diagram of the renal corpuscle illustrating the effective pressure from capillary to tubule as compared with capillary osmotic and tubule pressures

FACTORS AFFECTING FILTRATION

There are several factors that may increase or decrease filtration rate

1 Filtration pressure is one of the chief factors This may change because of an increase or decrease in blood pressure of the renal capillaries For example, in severe hypotension such as is found in shock where the systolic pressure may reach a low of 70 mm Hg the hydrostatic pressure in the glomerulus is not great enough to overcome the counter pressures and a condition of *anuria* (no urine) exists Increased urine flow may result from an increase in blood pressure—for example during excitement and exercise

2 The state of the renal arterioles is a factor in filtration rate The efferent arteriole may constrict and in doing so raise the pressure in the capillaries of the glomerulus which of course results in a greater rate This can occur even in hypotension so that normal urine formation can go on

3 Damage to the glomerular membrane, as sometimes happens in renal disease, will exclude the glomeruli as filtration units There will be less urine formation and blood and plasma proteins may pass through the damaged capillaries to appear in the urine This happens in glomerulonephritis and in eclampsia or toxemia of pregnancy

CHARACTERISTICS AND FUNCTIONS OF THE RENAL TUBULES

The structure of the renal tubules and their union with Bowman's capsule has been discussed (page 514) The glomerular filtrate which is similar to blood plasma but *without its proteins* after leaving Bowman s capsule passes through the three segments of the renal tubule to the collecting duct This filtrate is *extracellular fluid* Altogether, there are only 10 to 15 liters of extracellular fluid (blood plasma and tissue fluid), compared with 40 or 50 liters of *intracellular fluid* (within cells) Obviously if 125 cc of the extracellular fluid are formed every minute as stated above, and nothing is provided for its retention and reabsorption in the kidney, all of the extracellular fluid would be lost within a very short time However, this does not happen since there is a mechanism in the tubules by means of which water glucose salts and other substances needed by the body, are reabsorbed Of the 125 cc of filtrate produced all but about 1 per cent (a little over 1 cc) is reabsorbed by the cells of the tubule wall That reabsorption into the blood actually occurs is also suggested by the manner in which the efferent arteriole breaks up into capillaries which become closely associated with the tubules The so-called essential substances can then pass from the tubular wall into these capillaries

TUBULAR REABSORPTION

Reabsorption is the outstanding function of the renal tubule There are many *nonthreshold substances* such as creatinine, that normally are not reabsorbed by the kidney but are entirely excreted

Some of these substances are only partly reabsorbed most of them such as urea uric acid sodium chloride, and sodium bicarbonate, are excreted in fairly high concentrations The substances of *high threshold* are normally entirely reabsorbed unless the amount exceeds the threshold Glucose reabsorption is the classical example of this type

REABSORPTION AND EXCRETION OF GLUCOSE

The return of glucose to the blood via tubule cells is an example of the manner in which a substance important to vital processes of the body may be retained by reabsorption through the tubule wall The normal glucose

content of the blood is approximately 100 mg per 100 cc of blood (100 mg per cent) which means that in the 125 cc of glomerular filtrate delivered every minute, there are probably 125 mg of glucose In the normal individual, all of this is returned to the blood stream It is evidently accomplished at least partly, by enzymatic action which aids in the union of glucose with phosphate in the tubule cells In this form (the phosphate ester of glucose) it passes through the cell membrane into the cytoplasm to the opposite side of the cell where the glucose and phosphate separate The glucose then passes into the capillary

If glucose increases in concentration in the blood stream the same unit increase appears in the filtrate This is all reabsorbed by the cells of the proximal convoluted tubule as long as the concentration does not exceed 150 to 180 mg per 100 cc If the filtrate concentration is greater than this then the excess glucose appears in the urine The tubules cannot reabsorb it The appearance of glucose in the urine is called *glycosuria* *Hyperglycemia* is an increase in the glucose concentration of the blood

WATER REABSORPTION

This is a very interesting part of the excretory process Water is evidently reabsorbed to some extent in the proximal tubule Henle's loop and the distal tubule

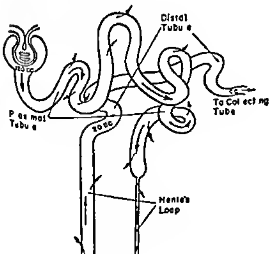


FIGURE 286

Illustrating the reabsorption of water in the renal tubule

Not only glucose, but sodium and other filtrate constituents are reabsorbed in the proximal tubule some water going through with them But

the filtrate passing into the thin segment is low in concentration compared to the original, that is, the fluid is hypotonic as it flows into Henle's loop. It is evident, then, that water passes through the walls of the tubule at this point in order to adjust the osmotic pressure to the surrounding interstitial fluid. This is sometimes referred to as *obligatory reabsorption*. The volume of fluid passing into the distal tubule is about 20 cc compared with 125 cc per minute in the proximal. All but about 1 cc of this is reabsorbed in the distal tubule. A so-called *facultative reabsorption* takes place in these tubules, being regulated according to the body's need. This is an active reabsorption process (that is, work is done) dependent upon a hormone produced in the posterior pituitary. By activation with this hormone the cells in the tubular wall are able to reabsorb large quantities of water and leave a highly concentrated solution (urine) behind. Sometimes the pituitary body does not function properly and the hormone is not produced in sufficient quantities to initiate reabsorption. Under these conditions very little water is absorbed by the distal tubule and a large quantity of urine with low specific gravity is produced, sometimes 15 to 20 liters per day, with a specific gravity of 1.001 as compared to the normal 1.015. This condition is known as *diabetes insipidus*.

TUBULAR SECRETION

In the mammalian kidney there is no proof that any normal blood constituents are secreted by the tubule cells into the glomerular filtrate as it passes through the lumen of the tubule. However, these cells have secretory powers in that glucose and such substances are secreted from them back into the blood stream; secretion can take place in either direction.

Some fish have no glomeruli, yet their urine is practically the same as that of organisms with glomeruli. The only manner in which this could happen is by secretion. In these fish the tubule cells secrete the excretory materials into the lumen of the tubule.

Dyes such as phenol red are secreted by tubule cells, and evidently penicillin is excreted rapidly from the body in this way.

It is evident, therefore, that the mammalian kidney has the power to secrete but seems to have lost this power for normal excretory constituents.

DIURESIS

Any increase in urine flow above the normal is called *diuresis* and any substance that causes this increase is a *diuretic*. Generally, diuresis can be produced in two ways: (1) by decreasing the reabsorptive ability of the tubular cells, and (2) by increasing the filtration rate.

A decrease in reabsorption is produced by such diuretics as sodium sulfate, urea, ammonium salts, and salyrgan (a mercurial compound)

Filtration rate may be increased in several ways (1) The filtering surface, itself, may be enlarged by an increase in the number of active glomeruli This is accomplished by dilation of those afferent arterioles of the glomerulus which have been closed, for it is doubtful that, normally during life all glomeruli are ever open at the same time (2) Filtration rate will increase if the blood pressure rises in the renal capillaries, no matter what the cause (3) A decrease in the protein content of the blood will reduce the osmotic pressure and thus, the hydrostatic pressure has a greater effect producing more filtrate

Caffeine and theobromine (a constituent of cocoa) appear to exert their diuretic action mainly by causing vasodilation in the blood vessels and hence increasing the filtration rate

Ingestion of large quantities of water or alcohol will increase urinary out put The extra water is thrown off within a few hours and most of it within two hours There is no evident diuresis until 30 to 60 min after drinking water

MICTURITION OR URINATION

Although the act of voiding urine is reflex in nature, it is controlled to a certain extent by the will It can be initiated or it can be interrupted or withheld, by voluntary action A desire to urinate normally appears when the bladder contains from 200 to 300 cc of urine It will hold as much as 500 cc

The urine of the bladder has the same composition as the fluid of the collecting tubules of the kidney From these tubules it passes into the pelvis of the kidney and drains into the ureter, which carries it to the bladder The ureters accomplish this by means of peristaltic waves that appear at the rate of one to five per minute

The bladder and sphincter muscle are under control of fibers of the autonomic nervous system Sympathetic fibers inhibit contraction of the bladder and constrict the sphincter separating the bladder from the *urethra* During micturition parasympathetic fibers cause an increase in tone of the bladder musculature and relaxation of the sphincter muscle Voluntary action also aids in micturition This consists mainly of contraction of the abdominal muscles while holding the diaphragm in a contracted state to prevent the abdominal contents from being forced upward The abdominal muscles bring pressure to bear on the abdominal viscera which in turn press against the bladder, forcing the contents out through the urethra

Micturition is purely a reflex action in infants Higher centers have no control over micturition until the child is about one and a half or more years of age Sometimes in the adult certain diseases or injuries (such as cutting the spinal cord) may bring about isolation of the bladder from the control of higher centers Urination then reverts to a pure reflex and voiding of urine occurs even though the sensation has not been felt

Today one of the first things a physician does when examining a patient is to analyze his urine By doing so he may find a clue to some abnormal condition in the patient Perhaps the first to make use of urinalysis was Richard Bright an Englishman who in 1829 discovered that certain patients with dropsy had a substance in their urine that coagulated like egg white when it was boiled This condition is still commonly referred to as Bright s disease The coagulated material is serum albumen which normally does not appear in urine but in nephritis because of injury to the nephrons it passes through the glomerular membranes along with other blood constituents

ADDITIONAL READING

Prosser C L *Comparative Animal Physiology* (Saunders 1950) ch 7 Means of nitrogen excretion by vertebrates and invertebrates

Smith H W *The Kidney Structure and Function in Health and Disease* (New York Oxford University Press 1951) Detailed accounts of human kidney function

Part Eight

ENDOCRINE GLANDS and REPRODUCTION

38

Hormones and the Endocrine Glands

PRODUCTION OF HORMONES IN PLANTS

HORMONES are chemical coordinators. They are organic substances which are produced by cells or organisms in which they perform specific regulatory functions.

The amount of hormone necessary to bring about a particular action is in most cases almost infinitesimal.

Plants need certain hormones for coordinated activity in growth and responses of various sorts. A well known plant hormone is *auxin*. This is produced in the tips of certain plants and accelerates the elongation of the plant. This is not the only location where auxin or phytohormones are produced; buds, root tips, leaves, green algae, and mammalian urine are also good sources.

During elongation of plants or plant structures by the action of auxin cell division is not necessarily involved, but instead there is a lengthening of the cells themselves as though they were able to take on more water (there are other hormones that function in cell division). Evidently this hormone is produced more rapidly by the cells on the shaded portions of a plant where they are protected from direct light rays. It is in this manner that a plant is enabled to turn toward the sun.

FIGURE 287

The plant bends toward the sun because more auxin is produced on the shaded side, causing the cells to elongate.

PRODUCTION OF HORMONES IN INVERTEBRATES

Apparently many invertebrate animals produce hormones comparable in their action to some of those produced by vertebrate animals; examples are adrenalin, acetylcholine, and estrus producing substances. At least injection of extracts of some of the invertebrates leads to actions similar to those produced by adrenalin, acetylcholine, and so forth.

It has been demonstrated that there is within the cells of some protozoan species a natural mechanism regulating growth and producing a hormone like substance which in low concentration accelerates growth and reproduction In high concentration the same hormone may retard and inhibit growth in protozoans It is likely that the size of cell populations is regulated in this manner

Metamorphosis and molting or ecdysis (page 37), of insects are controlled by hormones produced by special bodies or glands located near the brain or anterior ganglion

Color changes in animals are brought about by hormone action, the manner in which this is accomplished varying in different forms In certain *Crustacea* (for example, the shrimp), a definite gland, the *sinus gland*, is present endocrine in its action and comparable to endocrine structures of higher animals This gland is situated on the ventral and slightly lateral side of the eyestalk It has been shown that there is a connection existing between the eyes and color changes in these organisms The changes, definitely due to hormonal and not nervous action, are accomplished rapidly This can be demonstrated by injecting blood from a crustacean which has turned dark in the absence of light, into another which is light adapted thereby causing the second organism to turn dark

PRODUCTION OF HORMONES IN VERTEBRATES

The hormones most common to us are those produced by the endocrine glands An *endocrine gland* is a ductless gland which secretes its substance

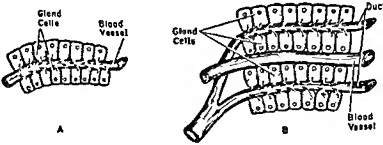


FIGURE 288

Basic structure of an endocrine gland A and an exocrine gland B Arrows show direction of secretion

directly into the blood stream, thus ensuring its distribution to all parts of the body An *exocrine gland* secretes its substance into ducts which collect it and carry it to some other part of the body For example, the salivary

glands are exocrine and pour their fluids into the ducts which lead to the mouth.

The study of the structures and the secretions of the ductless glands along with the effects of their secretions on organ and animal behavior constitutes the subject of *endocrinology*. This field has now become so extensive that only a few of the more important facts concerning these glands can be presented here.

The endocrine glands receive food materials and oxygen and get rid of their wastes in the same manner as other body tissues, using some of these materials to manufacture their hormones. These are then secreted directly into the capillaries surrounding the glandular tissue, there being no ducts into which the secretions can pass. Thus an experienced observer may judge a gland to be an endocrine structure if it has secretory cells but no ducts. The pancreas, for example, was known to be an endocrine structure for many years before insulin was discovered.

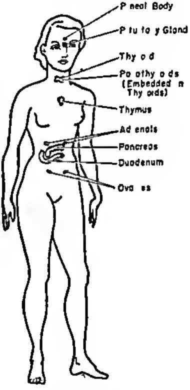


FIGURE 289

Approximate locations of the common endocrine glands.

The usual means of testing a glandular structure for endocrine action is (1) to remove the organ from an animal and note the effects, if any, on bodily function, and (2) if such disturbances occur, to attempt to counteract them by injecting extracts of the suspected endocrine gland. If definite deficiency symptoms follow the removal of the gland and if the body functions are restored to normal by administering suitable extracts, it may be called an endocrine gland.

Certain generalizations may be made concerning the action of endocrine secretions (except for the thyroid and parathyroid): (1) they pass from the blood vessels into the tissue cells rather rapidly, and (2) they are readily destroyed in the blood stream. If they did not pass rapidly into tissue cells, the response would be too slow, and if they were not destroyed readily, the response would be too prolonged.

The important endocrine structures in vertebrates are: (1) those of the mucosa of the gastrointestinal tract, (2) the thyroid, (3) the parathyroids, (4) the lobes of the hypophysis or pituitary body, (5) the thymus, (6) the

pineal body, (7) the adrenals (medulla and cortex), (8) the islet tissue of the pancreas, and (9) the gonads (testes and ovaries)

THE HORMONES OF THE GASTROINTESTINAL MUCOSA

The presence of proteins in the stomach seems to stimulate the secretion of *gastrin* a hormone produced in the walls of the stomach The hormone is carried by the blood stream through a complete circuit and on its return to the stomach it stimulates the gastric digestive glands to greater secretion of pepsin and hydrochloric acid

Secretin is a hormone produced by glandular cells in the walls of the duodenum The presence of acid in the stomach contents flowing into the duodenum is evidently the chief factor in liberation of secretin It then passes into the blood stream by means of which it is carried to the pancreas where it excites the exocrine part of the gland to produce more pancreatic juice containing enzymes Secretin is also believed to stimulate the gall bladder to contract and possibly to so affect the intestinal glands that more intestinal juice is produced and poured into the intestinal lumen The gall bladder however is stimulated chiefly by another hormone of the mucosa *cholecystokinin*

THE THYROID GLAND

The thyroid gland in man a bilobed structure the lobes of which are connected by an isthmus weighs approximately 25 g It lies ventral in relation to the trachea immediately below the larynx and is abundantly supplied with a network of blood vessels—an indication of the comparatively large quantities of blood that flow through it

As far as is known no special organ in the invertebrates resembles the thyroid gland in development or structure In the tunicates a pharyngeal groove the *endostyle*, has been called the forerunner of the thyroid gland of the higher vertebrates However this relationship appears to be an anatomical one since extracts of endostyle tissue possess no thyroid activity

The functional units of the thyroid are the follicles composed of a lining of cuboidal epithelial cells surrounding a central mass of colloidal material The colloid a rather viscous protein secreted by the epithelial cells combines with iodine to produce the hormone During periods of secretion the colloid passes from the follicle and the epithelial cells become elongated

Thyroid secretion plays an important role in metabolism as well as in

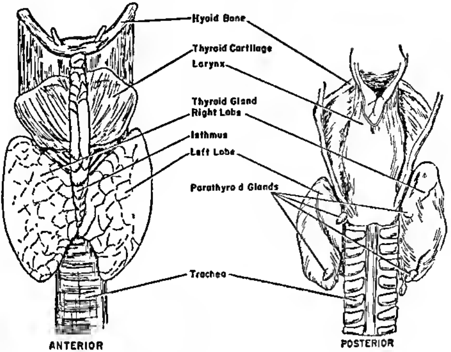


FIGURE 290

The thyroid and parathyroid glands Left front view of the thyroid gland right rear view showing the location of the parathyroids

development An increase in hormone concentration causes metabolic processes also to increase which is essential for proper development These functions are very well illustrated by development in the frog This animal has a thyroid gland on each external jugular vein, the glands are red in color because of the large number of blood vessels running through them The hormone is essential for metamorphosis from tadpole stage to the adult frog If the thyroids are removed from the tadpole it does not metamorphose but continues to grow, eventually becoming giant like in size On the other hand, if young tadpoles are given excessive quantities of thyroid gland or extract, they pass rapidly from the tadpole to the frog stage—so rapidly, in fact, that

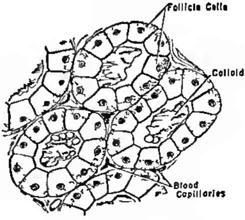


FIGURE 291

Microscopic view of the spherical follicles of the thyroid gland

they do not have time to grow in size but remain tiny frogs often no larger than houseflies.

DEFICIENCY OF THYROID SECRETION (HYPOTHYROIDISM)

In man, thyroid deficiency symptoms depend upon the age of the individual. Occasionally, in infants and young children a condition known as *cretinism* makes its appearance. Cretinism is a congenital deficiency, usually due to poor development of the gland during fetal life. The condition is characterized by retarded growth and poor bone development, slow heart rate, low basal metabolism (hypothyroidism), subnormal intelligence, marked obesity, and a noticeable flabbiness of the tissues.

FIGURE 292

Cretinism This patient was forty two years of age with an I Q of twelve (From Greisheimer, *Anatomy and Physiology*, by permission of J. B Lippincott Co)

Remarkable changes can occur in cretins if thyroid treatment is started early enough. Usually, ground dried sheep thyroids, in the form of pills, are used for oral treatment. A cretin may soon show mental alertness and normal development; this normal condition may be maintained throughout life by continued, proper administration of thyroid. If treatment should cease, the original symptoms will return (except that stature does not retrograde to that of childhood).

In adults, symptoms comparable to those of cretinism sometimes make their appearance if there is an insufficiency of thyroid secretion. The condition is known as *myxedema*. The person has, of course, grown to his fullest extent and has developed properly so that the deficiency does not change these particular characteristics. In other words, growth defects are not apparent. The symptoms are: puffiness or edema, especially about the face and hands, low basal metabolic rate, and a depressed mental state. These symptoms disappear upon feeding thyroid.

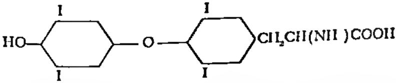
Another abnormality, due to a deficiency within the gland itself, is *simple* or *colloid goiter*. This condition generally appears in regions having an unusually low iodine content in the soil and water, and is characterized by swelling of the thyroid The enlargement is caused by the distention of

FIGURE 293

Simple goiter (From Selye *Textbook of Endocrinology* Second Edition by permission of Acta Endocrinologica Inc)

the follicles with colloid the lining cells becoming stretched and flattened The gland seems to attempt vainly to make up for low iodine content by forming more colloid but actually the material has no further supply of iodine upon which to draw Adding traces of iodides to drinking water or mixing them with table salt has greatly alleviated the condition of goiter in the Great Lakes area of the United States as well as other parts of the world where there is a low iodine content in the soil Because of the presence of iodine in sea water and seaweeds it is found that marine fish and other sea animals have comparatively high concentrations of iodine in their tissues Those persons living near the seashore therefore seldom experience the results of a deficiency of this element

Within the gland a substance called *thyroxine* is produced It was synthesized in 1927 and has the following formula



As thyroxine is formed in the gland it is combined with a protein (globulin) and is stored in the colloid of the follicles as *thyroglobulin* Under certain conditions the thyroxine is released from this combination

and goes into the blood stream, thyroglobulin does not appear in the circulation. Thus, thyroxine may be referred to as the circulating hormone, thyroglobulin is the form appearing in the gland.

HYPERTHYROIDISM. EXOPHTHALMIC GOITER

Hyperthyroidism is caused by an excess of thyroid hormone in the blood. In individuals suffering from this condition, the metabolic rate is high, nervous disorders are very apparent, and there is an accelerated heart rate.

In some types of hyperthyroidism there is a characteristic bulging of the eyeballs, a condition referred to as *exophthalmic goiter* or Grave's disease. Sometimes the gland enlarges but the enlargement is entirely different from that of simple goiter being due to hyperplasia. The disease is often fatal if not checked in time; this is accomplished by partial removal of the gland proper or by tying off some of the blood vessels leading to the gland. Certain drugs, such as thiourea and thiouracil, are used to depress thyroid function. They do not prevent thyroid hormone already present in the body from exerting its effect, but, instead, inhibit further thyroxine formation. Their usefulness in treatment of hyperthyroidism rests in the ability to regulate dosage to the individual's needs, thus in many cases, surgery is avoided. Generally, the administration of thiouracil is only a means of treatment, and not a cure, for hyperthyroidism. However, there have been reported instances of continued normal thyroid function after discontinuation of drug administration.

FIGURE 294

Exophthalmic goiter (hyperthyroidism). (From Selye, *Textbook of Endocrinology*, Second Edition, by permission of Acta Endocrinologica, Inc.)

Some control over the thyroid gland is exerted by the anterior pituitary secretion which contains a thyrotrophic factor. This factor stimulates the undeveloped gland to normal development; the response is a *hyperplasia* or increase in cell number. There may also be a coordinated action between the thyroid and the adrenal glands. They seem to be antagonistic, for when the adrenals are removed, thyroid activity is increased.

THE PARATHYROID GLANDS

The parathyroid glands are not found in animals below the *Amphibia*, that is, they appear only in vertebrates leading a terrestrial life

which suggests that the hormone may function in salt retention (especially calcium salts) within the body During skeletal development in the higher forms there is a much greater need for minerals The parathyroid gland may furnish a means for rapid alteration of mineral balances—absorption and deposition—during periods of rapid growth Such radical changes do not normally exist in invertebrates

In man, usually two pairs of parathyroids are embedded in the dorsal part of the thyroid gland although there have been as many as twelve pairs described Occasionally accessory parathyroids may be found anywhere from the neck region to deeply within the thoracic cavity

The parathyroids are oval or bean shaped and the two pairs weigh about 0 5 grams Their secretion is referred to as *parathormone* or *parathyrin* The true nature of the substance is not known since it has never been isolated in pure form but it is thought to be a protein since it is destroyed by the proteolytic enzymes of the gastrointestinal tract it therefore cannot be administered orally

Hypoparathyroidism (or deficiency of parathyroid) sometimes develops as a result of pathological degeneration of the gland but in most cases it has been due to inadvertent removal of the parathyroids during thyroidectomy The true action of parathormone is still rather obscure but its deficiency results in a lower blood calcium and an increased excretion of calcium by way of urine and feces This would suggest an all important function in calcium balance The content of this ion in the blood of a person suffering from hypoparathyroidism is reduced within a day or two from an approximate normal value of 10 mg per 100 cc of blood to 7 mg Muscle spasms or tetany soon make their appearance and the animal loses control of its muscles When the value is lowered to 5 mg of calcium per 100 cc death usually results

Sometimes in children symptoms of parathyroid deficiency make their appearance as so called infantile tetany or children s fits at the same time defective bone growth and poor calcification of teeth are noted

In experimental animals in which tetany has appeared as a result of parathyroidectomy injection of calcium salts will cause an immediate cessation of the spasms The effects of injecting the hormone may be so slow that the animal usually dies but if it is administered along with calcium it will prolong life Injection of parathormone into a normal animal causes an increase in the calcium level of the blood (hypercalcemia) and an increase in phosphorus excretion with a consequent decrease in serum phosphorus concentration

The action of the parathormone is in some ways similar to the action of

vitamin D One of the outstanding similarities is the increase in calcium content of the blood This may be owing to increased absorption from the intestine in normal or high vitamin D concentration, whereas in high concentrations of the hormone, calcium is drawn from the bones There is also some evidence to show that vitamin D is essential to normal parathyroid action or secretion

Some times tumors form on the parathyroids and cause oversecretion which is evident by the appearance of the symptoms produced by hyperparathyroidism It is dangerous to raise the blood calcium level above 12 mg per 100 cc

THE HYPOPHYSIS OR PITUITARY GLAND

The hypophysis or pituitary gland, is situated at the base of the brain It is about the size of a pea, weighs approximately 0 5 g and is attached to the brain by means of a stalk called the *infundibulum* It rests in a depression of the sphenoid bone called the *sella turcica*

Two main portions of the pituitary are easily identified the *anterior* and

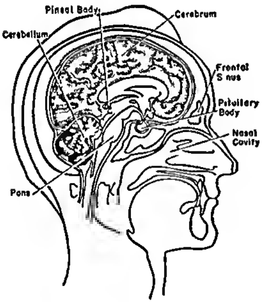


FIGURE 295

The relative positions of the pituitary (hypophysis) and pineal bodies

the *posterior lobes* The anterior lobe develops in the embryo from an invagination of the buccal cavity and is sometimes called the *pars glandularis* The posterior lobe which develops from a finger like projection arising from the third ventricle of the brain, is frequently referred to as the *pars nervosa* Other structures are also present such as the *pars intermedia* and the *pars tuberalis* the functions of which are not entirely clear

Removal of the hypophysis is very difficult and the results of earlier work on this gland were rather confusing because of injury to the neighboring brain tissue However, with practice and care, it can be removed without the immediate death of the animal Such an operation demonstrates the remarkable influence the pituitary gland has upon other endocrine structures in the body

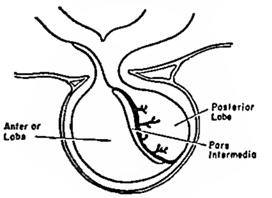


FIGURE 296

The pituitary body sagittal section

THE ANTERIOR LOBE

The exact number of hormones produced by the anterior lobe is not known Only a few of them have been isolated these being the somatotrophic, adrenotrophic, lactogenic, luteinizing, follicle stimulating and thyrotrophic hormones Of these, the first four have been prepared in pure, or nearly pure, form Other factors have been proposed but it is likely that some of the hormones produced by the anterior lobe have more than a single action

The growth promoting factor (*somatotrophin*) was not recognized as a specific substance for some time However, its isolation in pure form has led to studies proving that the material is stimulatory to somatic growth in general and especially in the areas of growth in the bones (epiphysis) Thus, if too much of the hormone is produced in children or if it is given in too great amounts to young animals, excessive growth occurs, the normal body proportions being generally maintained however This condition is referred to as *gigantism*

On the other hand if the anterior lobe is hypofunctional in the production of somatotrophin *dwarfism* results, in which case normal growth is inhibited to the extent that the mature individual is of extremely small stature, but of normal body proportions (Figure 297) Thus, the pituitary dwarf is readily differentiated from the cretin dwarf

Too great a secretion in adults leads to a condition known as *acromegaly* In this case, since only certain areas of bone are still capable of growth by enlargement, the increase in size is disproportionate enlargements are seen especially of the jaw, nose, hands, and feet Hypofunction in adults causes *cachexia* or *Simmond s Disease* in which there is a general emaciation along with many other irregularities and malfunctions

Follicle stimulating hormone (*FSH*) is the name given to the factor

FIGURE 297

Examples of gigantism and dwarfism caused by overactivity and underactivity, respectively, of the anterior lobe of the pituitary. Captain Gulliver is over eight feet tall while Major Mite is only three feet tall. (By permission of Keystone Illustrating Service.)

generally associated with the stimulation of the immature follicles of the ovaries to effect the development of mature ova. Sexual precocity can be established easily in young immature female mice or rats upon injection of this material. Such females may mate when only fifteen days old. Results with male mice are not so striking, although injection into males whose genitalia have atrophied (because of removal of the pituitary) will restore the organs to normal condition, after which spermatogenesis occurs and normal litters may be sired.

Luteinizing hormone (*LH*), another factor produced by the anterior pituitary, evidently influences ovulation and production of one of the sex

hormones within a portion of the ovary It had been proposed that probably a separate factor was responsible for stimulation of the production of male sex hormones in the testes Since this would involve a stimulation of the interstitial cells of the testes which evidently produce the male sex hormones the material was called ICSH (interstitial-cell stimulating hormone) However more recently it has been generally accepted that probably LH satisfies the function of the proposed ICSH in the male, and that they may be one and the same thing both are commonly called LH

The *lactogenic* hormone or *prolactin* causes secretion of milk in the mammary gland It has no effect upon breast development this must occur before the prolactin can act The female sex hormones *estradiol* and *progesterone* induce growth and development of the breast Progesterone also inhibits the action of the lactogenic hormone, the inhibition not being removed until the end of pregnancy when the progesterone concentration is reduced considerably At that time large amounts of prolactin find their way into the breast and milk secretion is induced LH FSH and prolactin have been referred to collectively as the *gonadotrophic hormones* Further discussion concerning the effects of these materials will be presented in the chapter on reproduction

The *thyrotrophic* hormone *thyrotrophin* causes increased production of the thyroid hormones as well as hyperplasia (an increase in cell number) of the thyroid gland

The *adrenocorticotrophic hormone* (*ACTH*) causes hyperplasia of the cortex of the adrenal gland and a greater secretion of the cortical hormones An interesting coordination exists in the presence of ACTH and the adrenal cortex hormones the adrenal cortex hormones resulting in inhibition of ACTH production However if cortical hormones are produced in smaller amounts ACTH is produced in greater amounts thus effecting a stimulation of the adrenal cortex Evidently a similar mechanism is functional in production of thyroglobulin and thyrotrophic hormone

factor, increasing fat metabolism, has also been proposed The possible actions of other factors—*parathyrotrophic, adrenomedullotrophic,* and *thymotrophic* hormones—are evident from the names It is difficult to say that these materials actually exist In many cases, the actions have been attributed to combinations of known anterior lobe hormones and to the influences of factors produced by the adrenal cortex upon stimulation by ACTH

THE POSTERIOR LOBE

The secretion of the posterior lobe contains several hormones, all present in the extract of the gland which is called pituitrin If the latter is injected into a mammal, the following effects may be observed

1 An *antidiuretic* effect thought to be due to stimulation of the renal tubules so that they reabsorb more water and thus inhibit diuresis Normally, then, this principle is concerned with the *water balance* of the body

If there is a deficiency in secretion of the antidiuretic hormone, a condition known as *diabetes insipidus* makes its appearance This is characterized by the excretion of large amounts of urine with a very low specific gravity, 10 to 30 liters of urine may be excreted per day (polyuria) with a consequent incessant thirst and frequent water intake The concentration of waste materials is very low in such urine If pituitrin is injected into a person suffering from this condition, it diminishes the great water loss through the kidneys by increased tubule cell absorption Under normal conditions, during periods when water is withheld, there is an increase in the secretion of the antidiuretic principle which aids in the conservation of water

2 A *vasopressor* effect by way of constriction of the arterioles The factor *vasopressin* or *pitressin* acts upon smooth muscle, causing it to contract This contraction of the smooth muscles of the arterioles brings about a rise in blood pressure It also stimulates the smooth muscle of the gastrointestinal tract, the urinary bladder, and other organs This factor usually possesses an antidiuretic effect as well, which has led to the proposal by some that vasopressin and the antidiuretic factor are one and the same

3 An *oxytocic* effect produced by the hormone *oxytocin* or *pitocin* This factor stimulates the smooth muscles of the uterus, under normal conditions, evidently having its effect during childbirth Until that time, the uterus is not so sensitive to its action that is, during that period when progesterone is secreted in large quantities (the *corpus luteum* phase) (page 564)

Oxytocin (contained in pituitrin) is sometimes used during labor or even

to induce labor. An excessive dose given injudiciously may cause such violent contractions that the uterus may rupture or the fetus be injured or killed; with proper dosage, however, it is safe.

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Hormones and the Endocrine Glands—continued

THE THYMUS

During youth the thymus is a rather large gland surrounding the lower end of the trachea near the heart. It increases in size up to puberty, but normally tends to disappear after sexual maturity. It weighs about 15 g at birth and contains much nucleoprotein. No conclusive evidence exists as to its true function, it is classed as an endocrine gland only because of its morphology.

Some investigators have suggested that it may be associated with body development up to the time of puberty, especially since it disappears at this period. Also, the fact that it contains so much nucleoprotein, has brought forth the suggestion that perhaps this material is used for early growth. It has been shown, however, that some animal species may grow and develop although deprived of their thymus glands.

Interesting results were obtained some fifteen or twenty years ago, when it was found that intraperitoneal injections of thymus extracts in female white rats over several successive generations had a decisive effect on the maturity of the young rats. Normally, the rat is born without hair or teeth, and the eyes are not opened until the fourteenth day. However, in each successive generation of rats injected with thymus extract, a progressive increase was noted in the development of the newly born rats, until, at the end of the fifth generation, they were born with hair and teeth, and their eyes opened on the first day. These results have not been confirmed, however, and until they are, or until other results and interpretations are forthcoming, our knowledge as to the true function of the thymus must remain in the theoretical stage.

THE PINEAL BODY

The glandlike organ, known as the pineal body, is about 10 mm long in man and lies in the groove between the superior colliculi, immediately beneath the *corpus callosum* (Figure 295, page 535). As was true for the thymus, the only reason for discussing this structure here is

that morphologically it resembles an endocrine gland physiologically no known function exists

Some physiologists have claimed that in children destruction of, or loss of function of this gland by tumor growth may result developmentally in mental and sexual precocity However the results are too meager and conflicting as yet to draw any definite conclusions concerning its functions

THE PANCREAS

The pancreas is a long narrow gland which lies in the upper abdominal cavity behind the stomach from the spleen to the curvature of the duodenum Ducts from its various lobules made up of enzyme secreting cells unite to form the main duct (*duct of Wirsung*) which ends in the duodenum at an opening common to it and the bile duct These structures make up the exocrine part of the gland A stained section of the pancreas examined

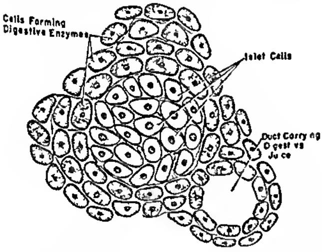


FIGURE 293

Section of pancreas showing islet of Langerhans (capillaries not shown)

microscopically shows, scattered among the lobules of the gland isolated clusters of cells that fail to stain in the same manner as the others These called the *islands* (or *islets*) *of Langerhans* are the endocrine parts of the gland secreting *insulin* The islets are most abundant in the tail of the pancreas but altogether they make up only three per cent of the weight of the whole gland The islets are more concentrated per gram of tissue in the pancreas of children than in that of adults

Numerous arterioles and capillaries surround each of the islets through the walls of which the hormone passes into the blood stream

Blood Sugar

Since blood sugar is so closely associated with insulin production and function it is necessary to consider the source of the glucose in the blood

The concentration of glucose in the blood stream remains fairly constant except after a carbohydrate meal when it increases considerably especially in the portal vein leading to the liver In the blood of the hepatic vein and other vessels of the body there is usually about 0 09 to 0 10 per cent glucose (90 to 100 mg per 100 cc of blood)

The liver can store glucose in the form of glycogen (up to 10 per cent of its weight) which is insoluble It takes most of the glucose which comes to it from the intestine by way of the portal vein and stores it until needed Since glucose is the primary source of energy in the bodies of animals there is a constant withdrawal of that stored in the liver once the muscles have used up their slight excess The glucose content of the blood is maintained at the expense of the liver glycogen This has been shown by experiments on fasting animals a period of starvation results in the disappearance of nearly all the glycogen from the liver

Hyperglycemia Glycosuria

Sometimes under certain conditions the blood sugar concentration may rise above the normal concentration of 90 to 100 mg per cent a condition known as *hyperglycemia* If the glucose should rise above 160 or 180 mg per cent it spills over in the kidneys and appears in the urine—*glycosuria* The kidneys have a certain threshold for glucose and if the concentration in the blood should exceed this threshold it appears in the urine Actually, the cells lining the walls of the kidney tubules can reabsorb only a limited amount of glucose from the glomerular filtrate

There are several ways in which hyperglycemia and glycosuria may be produced

1 As pointed out above if a meal consisting chiefly of carbohydrates is ingested there may be such a rapid absorption of glucose from the alimentary tract that its concentration in the blood becomes so great that some of it passes into the urine This is called *alimentary glycosuria*

2 During emotional stress such as competition in athletics fright or anger glucose may appear in the urine Excitement of this type causes the adrenal gland to secrete more adrenalin into the blood stream which in turn causes the liver cells to release some of their glycogen in the form of glucose This type is called *emotional* or *adrenin glycosuria* This is of course an emergency reaction that prepares an animal for fight or flight In either case an excess supply of glucose is thrown into the blood stream thus supplying a source of readily available energy

3 There is a form of glycosuria which is not found in nature except when a certain drug is injected into an animal The drug is called *phlorhizin*

and the consequent glycosuria is called *phlorhizin glycosuria* There is no evident hyperglycemia with this type since the drug only acts upon *the cells* of the kidney tubules and prevents them from reabsorbing sugar All the glucose that comes to them by way of the glomerular filtrate, passes on through to the collecting ducts and out with the urine

4 The type of glycosuria to which the layman usually refers is *diabetic glycosuria* which is pathological, the condition is known as *diabetes mellitus* The common symptoms of this disease are, along with *hyperglycemia* and *glycosuria*, *polyuria* (excessive urine excretion), *excessive thirst* due to dehydration, *increased appetite*, great *muscular weakness* and *fatigue*, *emaciation*, *mobilization of fats* as can be shown by examination of the blood and excessive production of *acetone bodies* by the liver (acetone is eliminated by the lungs) This causes an acidosis Low resistance to infection and poor healing of wounds makes surgical operations dangerous to diabetics

Action of Insulin

Diabetes mellitus is caused by a disease of the islet tissue of the pancreas in which there is an insulin deficiency However, malfunction in other endocrine structures, such as the anterior pituitary and the adrenal gland may also play a role in the appearance of the symptoms we usually associate with diabetes

When insulin is present in the blood stream, the tissues take up and utilize glucose readily, their ability to do this depends upon insulin concentration In other words, this hormone causes an increase in the oxidation of glucose Insulin is also essential in maintaining proper storage of glucose in the liver and muscles *How it carries out these functions* is still unknown

Normally, insulin secretion is controlled by the concentration of glucose in the blood stream, the greater the concentration, the more insulin produced The islet tissue is stimulated directly by glucose, coming to it by way of the blood stream, or it *is stimulated indirectly* by way *of the* "glycosuria center" of the medulla Impulses arrive at the islet tissue from the center by way of the vagi nerves and result in greater insulin secre

much longer. It had long been recognized that the pancreas was the seat of production of some substance that prevented diabetes, but, because of the protein nature of insulin, it could not be obtained from the pancreas. Whenever an extract of the gland was made in an attempt to isolate the hormone, the proteolytic enzymes from the exocrine part of the gland digested the insulin. Banting, in reading over the works of earlier investigators in which it was shown that the digestive part of the gland was destroyed if its ducts were ligated, figured correctly that the unchanged islet tissue should yield the hormone. His first success was secured by injection of the extract obtained in this manner into diabetic dogs. Later, a method of extracting the hormone from normal quickly frozen glands by acid alcohol was devised. This greatly simplified the work of extraction.

Hyperinsulinism

True hyperinsulinism results when tumors form within the islet tissue, excessive amounts of insulin are produced and, as a result, the blood sugar is decreased, a condition called *hypoglycemia*. In such a case, the only cure is removal of the tumor, but symptoms may be temporarily ameliorated if a person eats large quantities of carbohydrates.

Hypoglycemia may also result if too much insulin is injected. The symptoms are the same as those of true hyperinsulinism, but may be more dramatic because of the rapid onset. As the blood sugar level falls, a condition of mental confusion develops which is sometimes mistaken for the effects of alcohol. If blood sugar is reduced below 20 mg. per cent, severe convulsions may result and death will follow. Feeding sugar to a person suffering from an overdosage of insulin, or intravenous injection of sterile glucose solution if the individual is unconscious, may restore blood sugar levels toward normal and relieve the symptoms.

THE ADRENAL GLAND

The adrenal or suprarenal glands in man lie immediately above the kidney. There are two distinct parts to the gland, the *cortex* and the *medulla*; in other words, the adrenal gland may be subdivided into two glands. The cortex or outer part is derived from the same germinal tissue as the gonads; the medulla, as pointed out previously (page 172), has the same origin as the postganglionic fibers of the sympathetic division of the autonomic nervous system. In the elasmobranchs, the two glands are entirely separate, and it is claimed that analogous structures occur in species even as low as the annelid worms.

In man, the adrenals weigh *from 5 to 15 g*, about 10 per cent of the gland is medulla, the remainder, cortex

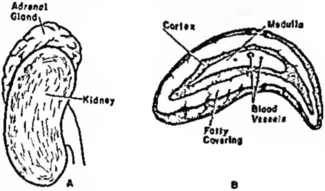
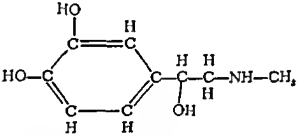


FIGURE 299

A position of adrenal gland above kidney, B, section through adrenal gland

The Adrenal Medulla

The cells of the medulla secrete *epinephrine* (*adrenalin*) which has the formula



It is related to the amino acid, tyrosine It is rapidly oxidized in neutral or alkaline solution, but is somewhat more stable in acid solution or in dry form

Epinephrine evidently has many functions, at least, it affects various systems of the body Its effects seem to be as widespread as those of the sympathetic division of the autonomic nervous system in fact, the two might even be considered as a single system, the *adreno sympathetic system* If the concentration of epinephrine is increased in the blood stream of a mammal by injection, the following effects are noted (1) A very noticeable increase in blood pressure, this is caused by stimulation of vasoconstrictor nerves leading to the arterioles (2) An acceleration in the heartbeat (3) A dilation of the bronchioles allowing the air to enter and leave the lungs more freely (4) An inhibition of activity throughout the gastrointestinal tract, except for the sphincter muscles (5) Dilation of the pupil of the eye, the radial muscles of the iris are stimulated, the circular muscles

inhibited (6) An increase in the glucose concentration of the blood owing to its effect on the liver cells, glycolysis is accelerated, which leads to glycosuria (emotional glycosuria) (7) Inhibition of contraction of the urinary bladder (8) A stimulating effect upon oxidative metabolism, this can be measured as basal metabolism (9) An increase in muscular power and a more rapid recovery from fatigue (10) A decrease in blood clotting time, which may be reduced to less than half that of normal

The adrenal gland therefore, reinforces the effects of stimulation of the sympathetic nervous system In spite of the numerous actions of epinephrine it is remarkable that an animal may live an apparently normal life when the adrenal medulla of both glands is removed This is at least partly, because of the fact that it is only a portion of the adreno sympathetic system and that the actions are continued by the sympathetic division of the autonomic nervous system

The Adrenal Cortex

If the adrenal glands are removed from an animal, it dies within a week or two It has been demonstrated that death is the result of the removal of the cortical rather than the medullary portion of the gland

In man a disease known as Addison s *disease* makes its appearance upon degeneration of the cortices The condition is characterized by the following symptoms (1) Cardiovascular disturbances such as low blood pressure, diminished blood volume, and weak heart which may lead to circulatory failure (2) Gastrointestinal disturbances such as loss of appetite anacidity (or lack of acidity), and diarrhea (3) A disturbance in the water electrolyte balance There is an increase in the loss of sodium and chloride and a retention of potassium in the blood the kidney is unable to re absorb the salts chiefly the sodium chloride, that filter through the glomerulus and consequently, blood concentrations are lowered (4) Retention of urea by the kidney, hence, an increase in its concentration in the blood The kidney tubule cells appear to reabsorb more urea than normally and hence the blood concentration increases (5) Bronzing of the skin usually appearing late in the development of the disease, this is caused by a deposition of pigment in the skin (6) Lowered basal metabolism (7) Great muscular weakness (8) Subnormal temperature

The best treatment for Addison s disease has been the administration of the whole cortical extract At one time it was thought that this contained but one hormone, *cortin* however several hormones are produced in the adrenal cortex One of them cortisone has received much publicity recently because of the discovery that it benefited patients with rheumatoid

arthritis In most cases, its action has been dramatic Patients who had not walked for many years did so within a few days after treatment However, if treatment is withdrawn, there is a return to the old condition

There is also an *androgenic* hormone which, if overproduced due to tumors or other functional disturbances, may lead to pseudohermaphroditism in young girls In boys, as well as girls, precocious sexual development may occur In adult women, it may lead to masculinization with an extreme development of hair, indicating an effect of an adrenal secretion on the gonads

The adrenal cortex is much richer in ascorbic acid than any other body organ, the reason for which is still unknown

THE GONADS

The gonads are the primary sex organs consisting of the *testes* in the male and the *ovaries* in the female The appearance of secondary sex characteristics such as hair growth, voice and muscular development, are dependent upon normal functioning of the gonads as is the complete development of the external genital organs In order to understand more clearly the way in which the sex hormones function, one should have some knowledge of the structures of the reproductive systems The organs involved in reproduction and the hormones associated with the processes are discussed in the following chapter

ADDITIONAL READING

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Reproduction

THE REPRODUCTIVE ACT in animals consists of a coordination of various functions by means of which the individual perpetuates the species to which he belongs. The individual dies but the species lives on—hence, the necessity that an individual have the capacity of reproducing himself.

Many animals die as individuals, once the sexual act is complete. This is especially true of the great class of insects. Other animals will go through extreme hardships in order to reach special breeding grounds; for example, the migration of salmon from the sea up fresh-water streams where they encounter almost impassable rapids and falls. Finally reaching their goal, they spawn and die. All of the eels in the world, when ready for breeding, start their migrations down the small fresh-water streams and rivers, where they have been living, and at length reach the sea. Eventually they collect at one particular area in the Atlantic Ocean southeast of Bermuda. The breeding areas of American eels and European eels overlap. Eels, also, die after breeding.

The migration of birds, although controlled to a considerable extent by climate, is carried out for the purpose of reproducing in a suitable location under proper environmental conditions. Birds migrate thousands of miles to accomplish these ends.

Other animals, as well, will suffer considerable hardships in order to accomplish the reproductive act.

REPRODUCTION IN LOWER ANIMAL FORMS

Although most animals perpetuate their species by *sexual* reproduction, some carry on an *asexual* type of reproduction. Asexual reproduction is found in the common protozoan, *Amoeba proteus*. There are no sexual differences whatever in an amoeba; when the organism has grown sufficiently large, its nucleus divides, which act is soon followed by division of the cytoplasm (sometimes referred to as *fission*). In this way, two new individuals are produced. Thus, each cell represents an individual organism which, barring accident or sudden environmental changes, is immortal. The same can be said for most living cells if their environment can be maintained under conditions suitable for them. For example, tissue

cells from mammalian bodies may be carried in tissue culture, apparently, for as long a period as one wishes, if one has the patience to see that the environment within the culture solution is kept under ideal conditions

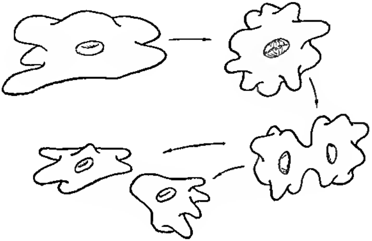


FIGURE 300

Asexual reproduction in *Amoeba* Two new organisms are produced by division of the cell

Sexual types of reproduction are found also in protozoan animals that is there is a temporary union (*conjugation*), at which time nuclear materials are exchanged In this manner, the characteristics of two individuals are intermingled (Figure 301)

Asexual reproduction occurs also in multicellular animals A good example is found in the fresh water coelenterate, *Hydra* It may reproduce by *budding* a process by which a miniature form of hydra is produced on the side of the parent (Figure 302) Eventually, the bud pinches off and begins to live as an independent organism Many other species also depend upon some form of budding *Hydra* also reproduces sexually both ova (or eggs) and sperm developing in the same individual Many more sperm cells are formed than ova this increases the chance that one of them will fertilize the ovum Such an animal in which both types of germ cells are formed and unite to start a new individual is called a *hermaphrodite*

The earthworm produces both ova and sperm but its ova are always fertilized by sperm from another individual

Hermaphroditism is not found in animals above the echinoderms In dividuals have either ovaries or testes and are known as females or males, respectively

Occasionally ova begin to segment and develop without fertilization

This is known as *parthenogenesis* and is common in some *Arthropoda*, although in most forms of this phylum (insects, crustacea, etc) the eggs are fertilized within the seminal receptacle of the female, after which they are expelled to the outside where they develop

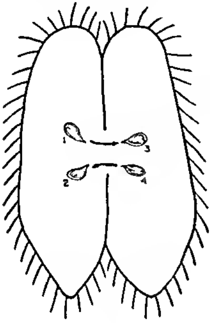


FIGURE 301

Diagrammatic representation of conjugation in *Paramecium* This is a sexual union and involves an exchange of nuclear materials The nucleus of each conjugant has divided and one part passes over into the other cell The two nuclei in each cell then unite

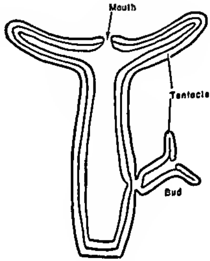


FIGURE 302

Diagram illustrating budding in *Hydra* a form of asexual reproduction

The honeybee is an excellent example of the parthenogenic type of reproduction If the eggs are fertilized, females (workers) are produced whereas those developing from unfertilized eggs are males (drones)

It was discovered many years ago that parthenogenesis can be induced artificially in some animals even though normally these animals never reproduce in this way The individuals that result from artificial parthenogenesis may develop into complete individuals The stimulus for cleavage of the egg may be chemical, electrical, or mechanical (as pricking the ovum with a needle)

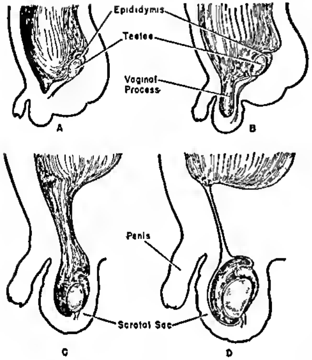


FIGURE 303

Descent of the testes into the scrotal sac A, about the third to fifth month, B sixth to seventh month, C, eighth to ninth month D, shortly after birth

Each testis consists of a mass of seminiferous tubules lined by cells specialized for the production of spermatozoa It has been estimated that in the two testes of an adult man there are about one thousand feet of seminiferous tubules Between these tubules, and surrounding them, are the *interstitial* cells which produce the male sex hormone, *testosterone* The tubules lead directly into the *epididymis*, also consisting of tubular structures in which the spermatozoa are temporarily stored

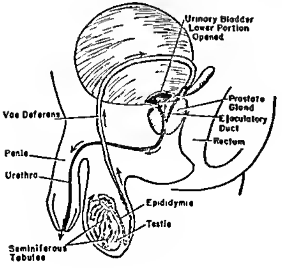


FIGURE 304

The male reproductive organs The path of the spermatozoa from the testes until they leave the body is indicated by arrows

A tube, the *vas deferens* (***ductus deferens***), leads from the epididymis to the *seminal vesicles*, which, along with the *prostate gland* and *Cowper's gland*, secrete the *seminal fluid*. When the spermatozoa mix with this fluid they begin very active movement, in which condition they are ejaculated. The *ejaculatory* duct leads into the urethra which carries the semen to the exterior.

MAMMALIAN SPERMATOZOA AND OVA

The male reproductive cells, or spermatozoa of mammals, are produced continuously by the spermatid cells of the seminiferous tubules, from the

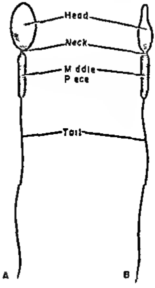


FIGURE 305

Sketch of human spermatozoon. A, top view. B, side view.

FIGURE 306

Copy of old drawing made of human spermatozoon. The observer thought he could see the shape of a "little man" in the head of the sperm and so developed the "homunculus" theory.

time of puberty (twelve to fifteen years) until death. Spermatozoa were discovered in the early part of the seventeenth century by Hamm, an associate of Antony van Leeuwenhoek. Hamm described them as "wriggling tadpole-like creatures" and Leeuwenhoek later claimed that he could actually see the shape of a human within the head of the sperm. This lead to his *homunculus* (little man) theory of reproduction. He believed that within the head of each spermatozoon was contained a small human individual which possessed sperm cells t

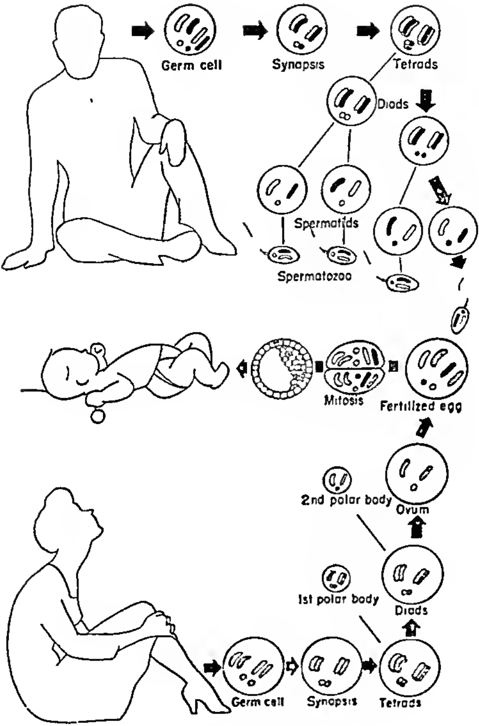
and so on *ad infinitum* In other words, according to his theory, the spermatozoa contained the life giving properties which developed into the embryo, the uterus being merely a place for its nourishment This idea lead to the use of the word *semen* (seed) for the fluid that is ejaculated during copulation

Spermatozoa are produced by means of a special type of cell division called *meiosis*, or reduction division (the ovum is produced in the same manner), during which the number of chromosomes are reduced by one half the usual number This form of division is represented in Figure 307 In the germ cell (male or female) the homologous chromosomes pair up (*synapsis*) The chromosomes then reproduce themselves and for a short time exist as groups of four (*tetrads*) The cells containing the tetrads are called primary spermatocytes By means of meiotic division each tetrad splits into two *diads* which also divide by *meiosis* into *spermatids* Each spermatid containing a *haploid* (one half the original) number of chromosomes eventually differentiates into a spermatozoon This reduction prepares both spermatozoa and ova so that when they unite during fertilization the chromosome number is again the same as it had been before maturation which number in man is forty eight Actually there are twenty four pairs (except in the male where one chromosome, X, does not match any of the others)

In the case of the egg or ovum, however, only a single functional cell is produced from the original The same type of division takes place and in the same manner as in sperm production but at each division one large cell containing much food material and one very small cell are produced The small cell is called a *polar body* The first polar body divides to produce two Thus altogether, during the egg maturation, three polar bodies and one ovum are formed

After the spermatozoa are produced in the testes, they are carried to the epididymis and stored there They may remain alive for a month or two, after which they die and disintegrate unless carried to the exterior Once they mix with the seminal fluid they last only a few days It has been estimated that approximately one trillion spermatozoa may be produced by an individual within a lifetime and that the normal ejaculation contains 200 000 000 or more

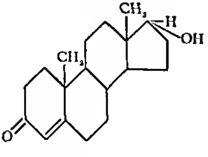
During copulation the spermatozoa may travel from the vagina to the uterus partly by their own flagellar movement and partly by suction action of the uterus They travel up the Fallopian tube (at the rate of about 6 in per hour), usually meeting the egg as it travels downward Fertilization occurs in the Fallopian tube Most of the spermatozoa die within a few


Germ cell
Synapsis
Tetrads
Diads
Spermatids
Spermatozoa
Mitosis
Fertilized egg
2nd polar body
Ovum
1st polar body
Diads
Germ cell
Synapsis
Tetrads

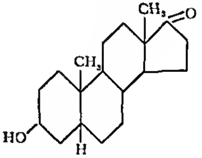
hours in the uterus and tube, but some may live for 30 to 40 hours The functions of the spermatozoa are twofold (1) They apparently initiate division in the egg by penetrating its membrane This can also be done by merely pricking the egg membrane (artificial parthenogenesis) (2) The nucleus of the sperm carries hereditary characteristics of the father which, with those of the mother, produce the characteristics of the new individual as it develops

THE MALE SEX HORMONES

It was not until quite recently that the endocrine function of the testes was proven, although the association of the testes with the functions and development of other structures has been recognized for 200 years or more In the early part of this century it was shown that if the *vas deferens* is ligated the germinal epithelium of the testes is destroyed with the result that no spermatozoa are produced, yet, the typical changes of castration (removal of testes) do not occur In other words, the interstitial cells of the testes, not harmed by ligation, produce a hormone which functions in the appearance and maintenance of secondary sex characteristics and in the sex behavior of the male This hormone is *testosterone*, which has been isolated in pure form It is metabolized to another closely related hormone called androsterone in which form it is excreted in the urine Both of them have been synthesized from cholesterol and are included under the general term *androgens* which also includes other potent agents, chiefly synthetic having actions similar to that of testosterone The structural formulae of these two hormones are



Testosterone



Androsterone

If an immature male animal is castrated it retains many of its infantile characteristics It grows normally but never becomes sexually mature For example, the *capon*, which is a castrated male chicken, develops the comb, wattles and plumage of a female although it does grow to a size even greater than normal

If the adult male is castrated, it loses many of its male secondary sex characteristics and there is a suppression of sexual activity.

The Gonadotrophic Hormones in Males

As was mentioned previously, the gonadotrophins do not appear to be sex specific Therefore, LH and FSH are effective both in females and males, exerting their influence upon specific tissues in each case

LH stimulates the interstitial cells of the testes to produce testosterone (page 539) For this reason, the stimulating material was at one time called ICSH (interstitial cell stimulating hormone), but it is now recognized as being identical with LH When testosterone has been produced in quantities in excess of that required, LH production is inhibited Thus, a natural balance is maintained

FSH stimulates development of the epithelial lining of the seminiferous tubules (page 538), thus bringing about normal spermatogenesis If the anterior pituitary in a young male is removed, it never reaches sexual maturity unless gonadotrophins are injected periodically The testes fail to develop and no spermatozoa are produced Likewise, the secondary sex characteristics do not develop and the animal appears as though castrated

THE REPRODUCTIVE SYSTEM OF THE FEMALE

The external genitalia of the human female are shown in Figure 308 The clitoris is homologous to the male penis and contains erectile tissue

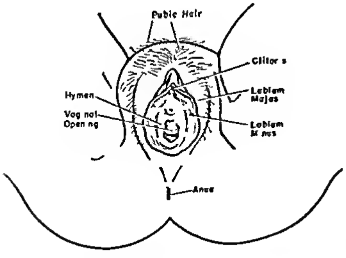


FIGURE 308
The external genitalia of the human female

Sometimes the clitoris undergoes too great a development and an organ quite similar to a penis is formed

The primary sex organs of the female are the ovaries. In mammals and most other animals they are paired structures that lie within the body cavity. The eggs or ova develop from the germinal epithelium that covers the ovaries. It has been estimated that several hundred thousand are

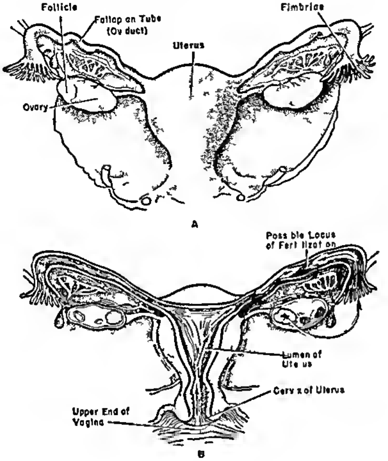


FIGURE 309

The internal genitalia of the human female. A, as seen from behind. B, with organs opened to show internal structures. Arrows indicate the route traveled by the sperm from the vagina to the Fallopian tube and that traveled by the ovum from the ovary to the Fallopian tube where the two fuse.

present in the ovaries at birth. They are primitive in structure, however, and can be noticed only as single cells within the mass of the ovary. During a human life span only about four hundred to five hundred of the ova get into the uterus.

As the ova approach maturity, a follicle is formed which becomes hollow and filled with fluid. At *ovulation*, the follicle containing the most mature

ovum ruptures and liberates the ovum into the abdominal cavity from where it soon passes into the Fallopian tube (or oviduct) evidently with the aid of the finger like *fimbriae* In the human, this occurs usually only once every twenty eight days

The walls of the Fallopian tube are muscular and are lined with ciliated cells, thus, by means of both muscular and ciliary movements, the egg eventually reaches the uterus

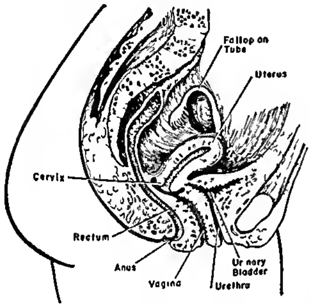


FIGURE 310

The human female reproductive system

The oviducts have become quite modified in mammals and it has already been noted (page 553) that in lower vertebrates, such as fish and amphibians the oviducts lead directly to the exterior The eggs are fertilized outside the body and are more or less 'on their own' after fertilization As is well known, fish and amphibians lay thousands of eggs but only a few develop into adults, since most of them are eaten by other animals

In the mammal, fertilization is internal The spermatozoa make their way up the Fallopian tube and fertilize the ovum as it passes toward the uterus Thus, the egg is partly developed when it reaches the uterus where it becomes attached to the walls of the latter Here it develops for a time, obtaining food substances and oxygen by absorption from the mother's blood stream

THE FEMALE REPRODUCTIVE CYCLE

Ovulation, which occurs, on the average, once every twenty-eight days during the sexual life of the human female begins at the time of puberty

and continues for thirty to forty years *Menstruation* follows ovulation and occurs at different periods in different individuals In most cases it takes place approximately fourteen days following ovulation The actual 'bleeding' period of menstruation lasts from three to five days occurring only when the ovum is not fertilized Before ovulation the *endometrium* or lining of the uterus grows considerably preparing itself for reception of the fertilized ovum If the ovum is not fertilized the superficial layer of this modified mucous membrane of the uterus breaks down Since it is highly vascular the breakdown and elimination of the tissue is accompanied by bleeding which is called the *menstrual flow* Thus menstruation does not occur during pregnancy or during the nursing period At about the forty fifth year of life the menstrual periods may show signs of irregularity and finally may cease altogether This is known as the *menopause* Ovulation ceases and consequently the uterine mucosa no longer prepares itself for reception of the ovum

THE ESTRUS CYCLE OF LOWER MAMMALS

In the lower mammals recurrent changes take place in the ovaries uterus vagina and mammary glands and there are recurrent variations in sexual urge these periods are referred to as *estrus* the period of sexual receptivity

There are several phases into which the estrus cycle may be divided (1) *Proestrus* is that time during which there are changes in the vagina uterus and mammary glands During (2) *estrus* or heat sexual desire is usually intense This is the phase when ovulation occurs In (3) *post estrus* the uterus and mammary glands develop further the uterus in anticipation of implantation of the ovum If fertilization has taken place implantation (pregnancy) occurs or in case the egg has not been fertilized pseudo pregnancy follows (4) *Anestrus* is the period of rest

In polyestrus animals such as the cow rat mouse and guinea pig ovulation is spontaneous several estrus periods occurring within each sexual season In the rabbit gray squirrel and cat ovulation occurs only after coitus—*forced ovulation*

During estrus or immediately following ovulation occurs and since the female will receive the male only during this heat period the spermatozoa are injected into the uterus at about the same time as the ovum or ova reach it Estrus and menstruation differ in several respects for example ovulation occurs usually during estrus in lower mammals whereas menstruation as already pointed out occurs about fourteen days following ovulation in primates

THE FEMALE SEX HORMONES

Hormones Produced in the Ovary

In the follicular fluid of the ovarian follicle is a hormone called *estradiol* which is also a sterol closely related in chemical structure to the male sex hormones. It is produced by the cells surrounding the follicle. *Estrone* (*theelin*) is similar in action to estradiol and is found in urine. It is only about twenty per cent as potent as estradiol. They are collectively referred to as *estrogens*.

A change takes place within the mature follicle after it ruptures, and the egg passes into the Fallopian tube, the *corpus luteum* or "yellow body" developing from it. The follicular cavity becomes filled with a yellowish substance and the cells surrounding it now produce a hormone called *progesterone*. If fertilization occurs and the egg becomes embedded in the endometrium of the uterus, this hormone continues to be produced until parturition (or birth).

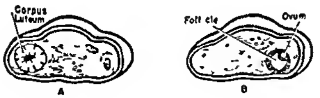
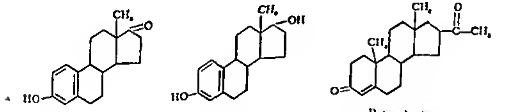


FIGURE 311

The appearance of the ovary. A, after the ovum from the old follicle has left the ovary and the "yellow body" has formed. B, when a new follicle has developed and migrated to the surface of the ovary.



Estrone Estradiol Progesterone

The hormone estradiol stimulates the development of secondary sex characteristics and the initial growth of the *endometrium* of the uterus in preparation for the ovum. It also initiates early growth changes in the mammary glands and prepares them for further action by other hormones.

Progesterone is the pregnancy hormone causing further growth of the endometrium as well as the vessels and glands associated with it. In other

words, it prepares the uterus still further for reception of the egg after the necessary priming action of estradiol

If the progesterone supply should be cut off for one reason or another during early pregnancy miscarriage soon follows The hormone is essential for the maintenance of pregnancy It also affects the mammary glands so that their development is completed by the time of parturition It has nothing to do with milk formation however That is the function of another hormone called *prolactin* produced by the anterior lobe of the pituitary body

Gonadotrophic Hormones of the Anterior Pituitary

Two hormones are produced in the anterior pituitary one of which has action on the follicle (*follicle stimulating hormone* or *FSH*) and the other on the *corpus luteum* (*luteal hormone* or *LH*)

The FSH acts upon the follicles of the ovary and stimulates their growth but does not alone lead to ovulation As the follicle grows the production of estradiol increases which has an inhibiting effect upon the further production of FSH and a stimulating effect upon the production of LH When the proper balance between FSH and LH is reached it stimulates maturation of the follicle which consequently finally bursts and sets the ovum free With further decrease of FSH and increase in LH production the *corpus luteum* appears This body remains in the ovary if the egg is fertilized and the hormone *progesterone* which in some way inhibits the production of FSH by the anterior pituitary is produced by the cells of the *corpus luteum* until parturition or birth some estrogen also is produced However, if the ovum is not fertilized the *corpus luteum* regresses and the hormone produced by it decreases to a point where it can no longer inhibit production of FSH Thus the follicle stimulating hormone increases other follicles begin to grow and the cycle is repeated

FERTILIZATION

Fertilization as already pointed out almost always takes place in the Fallopian tube The chances of fertilization if an ovum is descending the tube and spermatozoa are ascending depends upon the viability of the ovum and sperm Some claim that the human ovum must be contacted by the sperm within ten hours following copulation or fertilization does not take place At any rate the maximal survival period for human ova is about two days and that for spermatozoa about three days

The fertilized ovum begins its development in the Fallopian tube and within a few days after it reaches the uterus it is in the *morula* stage The lining of the uterus (the endometrium) has of course been prepared for the

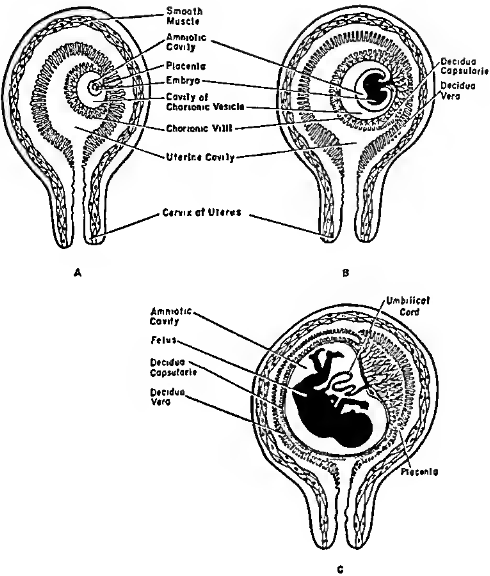


FIGURE 312

Successive stages in the development of the individual *in utero* A about three weeks, B, eight weeks, C four months Note the gradual decrease in the capacity of the uterine and chorionic cavities Early in the fourth month the uterine cavity is obliterated by fusion of the *decidua capsularis* and *decidua vera* The chorionic and amniotic membranes form the wall of the fetal sac; this is the membrane that breaks during labor allowing amniotic fluid to escape

fertilized egg by growth and vascularization The *embryo*, as the mass of cells is now called, is well supplied with proteolytic enzymes which seem to digest their way into the mucosa of the uterus, forming, in conjunction with it, a saucer like structure which is called the *placenta*

PREGNANCY OR GESTATION

Pregnancy begins with fertilization of the ovum and terminates approximately 280 days after the last menstruation. When a fertilized ovum becomes implanted in the walls of the uterus, it, in some manner, inhibits the occurrence of menstruation, the absence of which is usually the first sign that an ovum has been fertilized and implanted. However, other means exist for ascertaining a condition of pregnancy. Newer methods depend upon the fact that estrone, progesterone and gonadotrophins become very concentrated in the urine. If urine from a pregnant woman is injected into immature virgin rats, the uteri of the rats grow considerably and the change is very evident within a four-day period. This is the well-known Ascheim-Zondeck method. The Friedman test depends upon the fact that numerous bleeding spots appear on the ovaries of young virgin rabbits following such injections. There are still other methods; one of these utilizes female frogs, which lay their eggs within a few hours after injection of the pregnancy urine. The test that seems to be in greatest use today employs the male frog, which, when injected with urine from a pregnant woman soon releases spermatozoa. The frogs are placed in a beaker with a few cubic centimeters of solution in which the sperm are found.

THE PLACENTA

The placenta serves two purposes: (1) as an endocrine gland in the production of estrone, progesterone and gonadotrophin, and (2) as a means for exchange between mother and embryo. It produces sufficient quantities of various hormones with the result that, after the first or second month, the ovaries may be removed and pregnancy will go on to a successful termination.

When the developing embryo first becomes attached to the endometrium, food materials and other essential substances are absorbed directly from the surrounding capillaries. As it increases in size, however, this method is no longer adequate, and the placenta takes over these functions. As the embryo grows, villi are produced which invade the vascular areas of the endometrium and project into the large sinuses in which the maternal blood flows. These villi function in a manner similar to those of the intestines. The blood of the fetus flows through the villi of the placenta where it loses waste materials, notably urea and CO_2, and obtains food substances and oxygen by diffusion and then returns by way of veins to the fetal circulation (Figure 212, page 337). The embryo is, therefore, from the very beginning, a separate

and independent organism, with no direct mixture of its blood with that of the mother

PARTURITION OR LABOR

Parturition develops at the end of pregnancy During the last week, intermittent contractions of the uterus appear, which aid in placing the fetus in proper position for expulsion Finally, these contractions become very vigorous (*labor*), and consequently, tend to force the fetus to the outside It has not been proven that such contractions in humans are sufficient to expel the fetus without aid from the mother This aid makes its appearance in voluntary contractions of muscles such as respiratory, abdominal and pelvic muscles that ordinarily are used in defecation The factors involved in the appearance of vigorous uterine contractions are not clear Some have thought that since there is a degeneration of the *corpus luteum* at term and a consequent decrease in progesterone production, the latter no longer inhibits formation of the oxytocic factor of the posterior pituitary (page 540) This factor, as is already known, stimulates contraction of the smooth muscles of the uterus However, it has been found that during labor, the contractions go on, even when the posterior pituitary factor is missing

After its passage from the uterus, the fetus is still attached to the umbilical cord which commonly is ligatured and cut Later, further contractions of the uterus result in expulsion of the placenta (*afterbirth*) Some blood is lost because of the uterine sinuses being exposed after detachment of the placenta, but the contractions of the uterus normally check the blood flow before any serious loss takes place

Sometimes multiple births occur in humans Twins make their appearance about once in every 87 births, triplets once in every 7103 quadruplets once in every 747 000 and quintuplets, once in every 41 000,000

Multiple births may result from (1) the release of more than one ovum (multiple ovulation) and eventual fertilization or (2) the separation of the cells during early division of a single fertilized ovum Twins produced in this way from a single ovum are called *identical twins*, those produced by multiple ovulation, *fraternal twins*

LACTATION

Lactation occurs in the breasts or mammary glands, which are actually modified sweat glands Externally they are hemispherical in shape with a centrally located nipple, surrounded by the areola Both nipple and areola are pigmented the pigment which is pinkish in youth takes on a brown

color early in pregnancy. Internally, the breast consists of glandular and connective tissue.

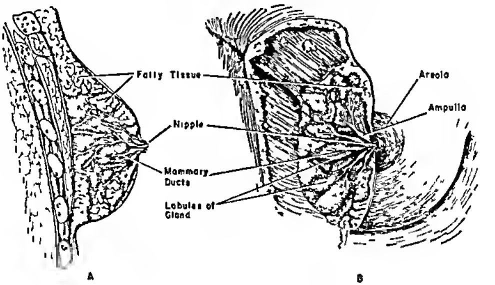


FIGURE 313

Structure of the breast or mammary gland. A, side view; B, front view.

It has already been noted that estradiol stimulates growth of the ducts in the mammary glands, and that progesterone stimulates growth of their alveoli.

The development of the mammary gland from childhood to maturity is illustrated in Figure 314. For the most part, the glands remain quiescent until puberty. Then, the follicles of the ovary begin to ripen, with a consequent increase in production of estradiol which initiates early growth of the breast. As ovulation occurs in the ovary, the *corpus lutea* are formed and produce progesterone. This hormone stimulates the breast to further growth and stimulates an increase in number and size of lobules and acinar structures. All this takes place during adolescence and prepares the breasts for the childbearing period. During pregnancy, with further production of such hormones, the breasts continue to enlarge greatly.

Estradiol and progesterone do not function in milk secretion. As already noted, this function is borne by *prolactin*, a hormone formed in the anterior lobe of the pituitary, but, before it can have its effect, the glands of the breast must first develop by action of estradiol and progesterone.

It has been suggested that prolactin is produced only after progesterone secretion decreases, which condition occurs toward the termination of pregnancy. During pregnancy, further development and increase in lobule formation takes place due to the action of progesterone produced by the *corpus*

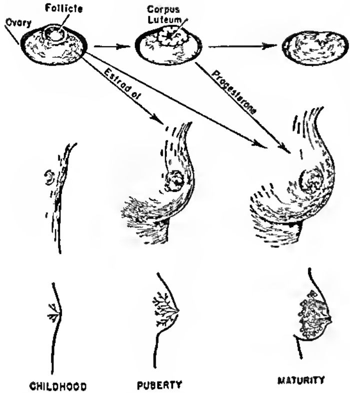
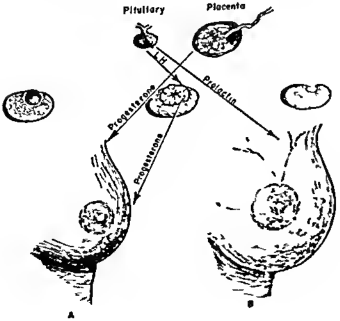


FIGURE 314

Development of the female breast from childhood to maturity At puberty the anterior pituitary hormone stimulates follicle development, which results in greater estradiol production This initiates growth of the breast Later when ovulation begins to occur with *corpus luteum* formation progesterone is secreted which stimulates further development of the breast to the fullness that is characteristic during the child bearing period

luteum which is augmented by a similar hormone that is produced in the placenta Toward the end of pregnancy the lumina of the tubules have dilated and begun to fill with colostrum which is the fluid that first appears following childbirth Colostrum consists of fat globules and special cells



Glossary-Index

abdomen vasoconstrictor fibers in 367 peritoneal arrangement in 471

abducens nerve *sixth cranial nerve motor for eyeball movements* 144

aberration *unequal refraction of light of visible spectrum by lens system of eye resulting in faulty vision* 226 227, chromatic, 227, spherical 226

absorption *process by which material is taken into cell or food passes from intestine into blood stream or lymphatic vessels,* 57

acinar structures 568

accessory nerve *eleventh cranial nerve motor and sensory to muscles of upper trunk* 144

accommodation *ability to focus vision on object so that it can be seen clearly,* 232 37

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acetone bodies 545

acetylcholine *chemical substance important in transmission of impulses along nerve and over many myoneural junctions* 179 180 343 451 528

achlorhydria *lack of acid secretion by parietal cells of gastric glands* 489

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acidity and blood buffers 421 control of by stomach 489

acidosis *condition within body in which pH of blood and tissues has less than normal but not truly acid value see pH*

acoustic nerve *eighth cranial nerve sensory for hearing and equilibrium* 142

acromegaly *condition resulting from excessive secretion of somatotrophin in adult characterized by enlarged jaw nose hands and feet* 537

ACTH *see* adrenocorticotrophic hormone

actin *protein of muscle fiber important in contraction process* 88

actinic *pertaining to light rays generally in ultraviolet range capable of evoking chemical changes in substances absorbing them*

action current *a change in electrical charge (electrical potential) at surface of muscle or nerve that passes in wavelike manner from point of stimulation* 85 and the impulse, 83 84 in muscle, 75, 82 84 negative 86 of nerve, 82 83 116 17

activator *a receptor, stimulation leads to reflex action not sensation* 186

adaptation of organism *ability to alter form or activity to withstand or make use of environmental conditions,* 8

adaptation of receptor *process whereby receptor becomes used to constant stimulus with gradual lessening of sensation* 189 90

Addison s disease *condition resulting from deficient adrenal cortex function characterized by cardiovascular and gastrointestinal disturbances bronzed skin, muscular weakness lowered metabolism and altered water and salt balance in the body,* 548

adenosine diphosphate (ADP), 96

adenosine triphosphate (ATP) *adenosine combined with three phosphoric acid molecules decomposition to release the phosphate groups results in release of great amounts of energy* 96, 126, in syneresis 99

adequate stimulus *stimulus that is specific for certain receptor as light for eye or air vibration (sound) for ear* 187

adenylic acid 96

adrenal gland *gland(s) lying anterior to kidneys control among other things salt balance and emergency reactions in body* 172 530 546 49 cortex of, 210 546 548 49 and heat production 426 and hormones 546 49 medulla of, 546 547 48

adrenalin *chemical substance formed by adrenal medulla and some sympathetic nerves* 174 179 528 and capillary 350 formula for 547 and vasomotor activity 370

adrenergic *producing adrenalin or sympathin* see autonomic nervous system, fibers of

in, 210, temperature sense in, 197, tetanus in muscles of 75, touch organs in, 191

insertion *movable point at which muscle is attached,* 100

inspiration (see *also* lungs, respiration), 381

insulin *hormone produced by cells in islets of Langerhans of pancreas, function is to regulate carbohydrate metabolism in body,* 543, 545 46

integument 24

intelligence, and organism, 157

intensity *property of sound that depends upon force with which air vibrations reach ear,* 188

internal anal sphincter *thickened circular layer of smooth muscle fibers at anal region that by constriction, normally retains material in rectum but is involuntarily relaxed during defecation,* 480, 481

internal respiration *gaseous exchange be*

invertebrates arginine phosphate in, 95 circulatory system of, 327 29, color vision in, 246, digestion in, 467 68, excretion in, 510 12, hormone production in, 527 28, muscle contraction in, 68 respiration in, 377, respiratory pigments in, 409, sound receptors in, 254, static organs 265, temperature sense in, 197, tonus in 78, vision in 231

in vitro *outside of body*

in vivo *in natural environment within body*

involuntary muscle, see muscle, smooth

ion *electrically charged (positively or negatively) particle formed when some substances are dissolved,* 116

iris *colored anterior portion of eyeball that regulates amount of entering light* and anterior cavity, 223 24, functions of 225, innervation of, 227 28, structure of 224

iron daily requirement of, 206, deficiency

stimulated by sound waves, but the temperature or the drug has such an effect that impulses are set up in the auditory nerves—hence, the ringing sound. These types of stimuli are said to be *inadequate stimuli*.

DIFFERENCES BETWEEN SENSATIONS

Different sensations are absolutely distinct in consciousness of them. Sight, smell, taste, sound, and touch are never confused; they can be separated in one's consciousness. These different sensory impressions are not referred to the brain but to the sense organ stimulated, that is, taste is referred to the tongue and sound to the ear. This difference between one sensation and another which separates them in consciousness is referred to as *modality*. Quality can also be distinguished within a modality. This simply means that in sound, for example, one can judge between a tone of low or high pitch, or in colors between blue, green, and others. However, the quality of one modality cannot be compared with that of another. For example, one cannot say that *this sound is of higher pitch than this taste is sweet*. Each sensation, therefore, possesses a modality that is absolutely specific for it and the quality within the modality can be ascertained. *Intensity* of sensation can also be distinguished within a certain modality, such as bright and feeble light of the same color or loud or weak sound of the same pitch.

must be added, and so forth, up to the physiological limit (about 1000 g) In the case of touch and pressure, then, the ratio is 30 1, for sound, it has been found to be 9 1, and for light, 120 1

ADAPTATION

Usually a decrement in response to a stimulus is referred to as fatigue, whereas the phenomenon is rather one of adaptation One seems to 'become accustomed to a stimulation It is true that fatigue may enter into the picture but, for the most part, in reference to action of the sense organs, one becomes 'adapted to a stimulus As previously stated (page 136), a stimulus applied to a sense organ results in a volley of impulses which proceed over the nerve to the central nervous system These impulses last for a brief space of time but, if the stimulus be continually applied, it is found that the rhythmical discharges of impulses diminish and may disappear completely Stimulation of touch receptors, for example by application of a disc of known weight to the skin surface is followed by a burst of impulses which continue for from 0 1 to 0 2 sec but disappear entirely by the end of 0 5 sec, although the same pressure is maintained continuously on the disc If slightly greater (or lesser) pressure is now applied to the skin, another volley of impulses follows which ceases at about the same time as the first In the same way, one becomes adapted to odors to the ticking of a clock and to the contact of clothes Even the retina becomes accustomed to a stationary object and in order to perceive it best, the eyeballs are kept moving constantly (though so slightly as to remain unnoticed) in order that the end organs may be stimulated intermittently

If this phenomenon were one of fatigue it should be more evident with the stronger stimulus, but actually the condition is most evident with weaker stimuli, that is a strong odor is detected for a longer time than a weak one If this were a fatigue phenomenon it would appear sooner, as well as being more evident, with the stronger stimulus Another argument against this being a state of fatigue is that the rapid decline in frequency of impulse discharge is not affected by a lack of oxygen, fatigue appears most rapidly in its absence Adaptation is a property common to receptors and is evidently a protective one, in the case of touch reception and the like, that is, certain receptors, after responding to a stimulus and conveying impulses over the nerves of the C N S, become adapted to that stimulus and are soon again ready to respond to a second similar stimulus On the other hand receptors for pain adapt very slowly, and so a harmful stimulus might be detected for a long period of time If adaptation to painful stimuli occurred as rapidly as that for tactile sensation one might by conscious effort with